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Review

Piezo1 and tissue fibrosis: insights into its role and potential for modulation

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Abstract

Fibrosis is a pathological process marked by excessive extracellular matrix deposition, ultimately resulting in irreversible tissue damage. This aberrant process manifests across multiple organs, including the skin, lung, cardiovascular system, liver, kidneys, and eyes. However, the underlying mechanisms driving tissue fibrosis remain incompletely elucidated, and effective therapeutics are still lacking. In recent years, increasing attention has turned toward the contribution of mechanical signals to fibrotic progression. Within this context, the Piezo family of mechanosensitive ion channels, recently identified as key mediators of mechanotransduction, has emerged as a compelling focus of investigation in diverse pathological settings. This review summarizes current evidence on the central role of Piezo1 in orchestrating fibrotic responses across various tissues. Moreover, we examine the application of Piezo1 modulators in experimental models and their potential to modulate fibrosis, thereby informing the development of novel antifibrotic interventions. By integrating mechanobiological insights into the study of fibrosis, this work highlights promising translational avenues for advancing therapeutic strategies and improving clinical outcomes in fibrotic disease.

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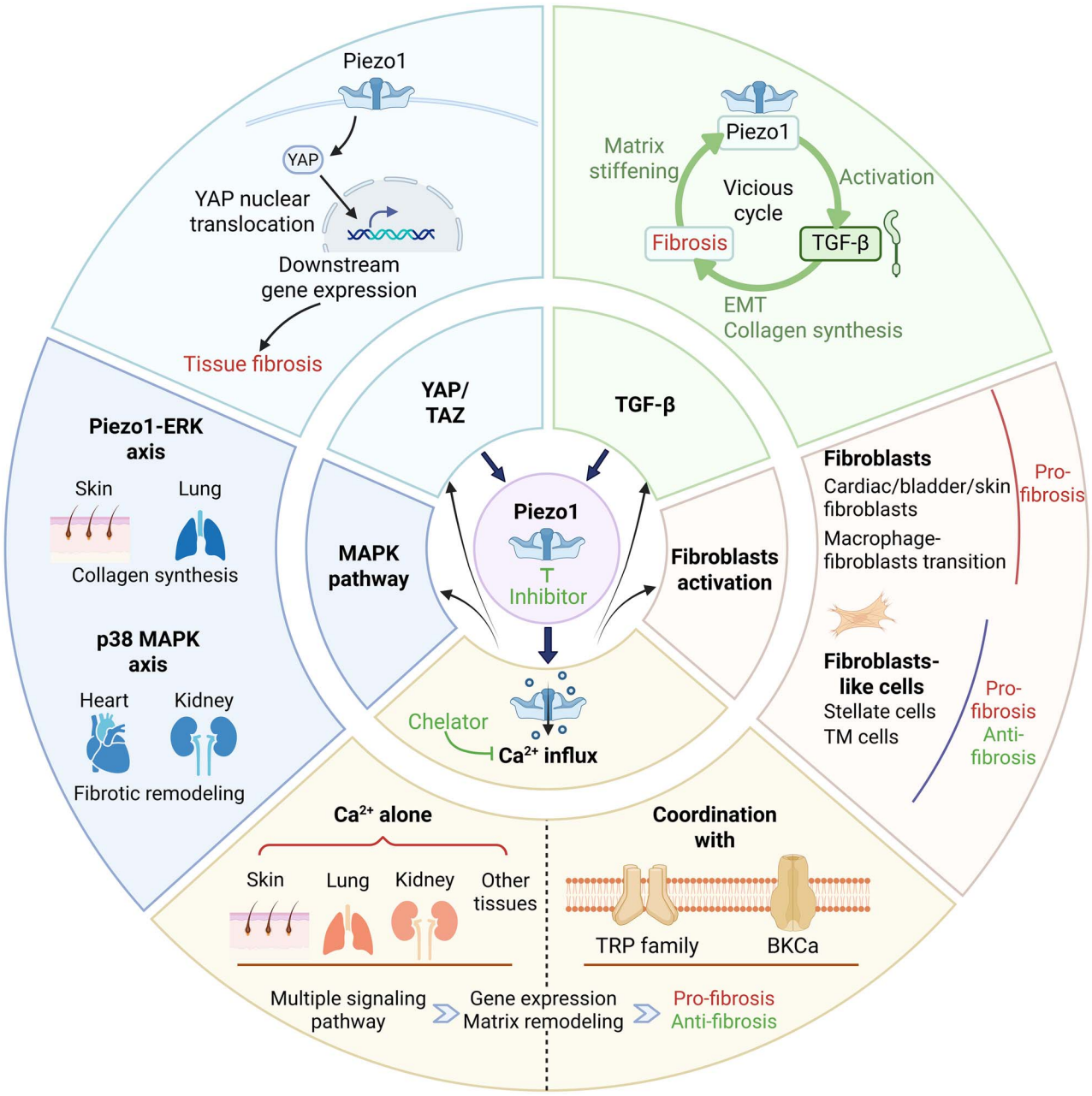
Graphical Abstract



Keywords: Piezo1; Fibrosis; Biomechanics; Extracellular matrix

Highlights

- This review systematically elucidates the role of Piezo1 in tissue fibrosis and provides a comprehensive overview of the pharmacological properties and potential applications of its modulators.
- It further explores the underlying contextual-dependent mechanisms of Piezo1's dual functions, laying a foundation for future research and the development of novel therapeutics targeting Piezo1.

Background

Tissue fibrosis represents a significant clinical challenge and a major threat to human health. It can arise from chronic inflammation, physical injury, or sustained m stress, affecting a wide range of organs. Due to its largely irreversible nature, fibrosis often leads to progressive and severe impairment of organ function. Inflammatory cells and fibroblasts are central mediators in this process [1, 2]. Taking skin fibrosis as an example, persistent inflammation, excessive activation of myofibroblasts, and aberrant extracellular matrix (ECM) remodeling can collectively drive ECM overaccumulation, culminating in scar tissue formation [3, 4]. This fibrotic repair represents a pathological variant of wound healing, characterized by uncontrolled replacement of normal parenchymal tissue with connective tissue, resulting in extensive remodeling, persistent fibrosis, and permanent scarring [5].

History of the correlation between mechanical forces and tissue fibrosis

Increasing evidence indicates that scar formation arises from cellular responses to mechanical cues within damaged tissues [5]. Mechanical forces, such as blood flow shear stress, ECM stiffening, and intercellular tension [6], are sensed by mechanosensitive proteins like integrins, which link the cytoskeleton to the ECM and mediate force transmission [7]. Myofibroblast contraction stiffens adjacent ECM, activating integrin $\alpha V\beta 3$ on macrophages and triggering nuclear translocation of nuclear factor of activated T cells 1 (NFATC1) and Yes-associated protein (YAP) to enhance fibroblast contractility [8]. Concurrently, mechanical traction activates latent transforming growth factor β (TGF-β) in the ECM, driving profibrotic gene expression [9].

This mechanical regulation extends to vascular fibrosis, where disturbed flow and low shear stress promote YAP/-transcriptional co-activator with PDZ-binding motif (TAZ) activation, fueling glycolysis, inflammation, and fibrosis [10, 11]. LSS also suppresses Krüppel-like factor 2 (KLF2) and endothelial nitric oxide synthase (eNOS), reducing nitric oxide while increasing endothelin-1, which together induce vasoconstriction and fibroblast activation [12]. Elevated hydrostatic pressure amplifies angiogenesis via fibroblast growth factor 2 (FGF2)-FGFR2 signaling, facilitating thrombogenesis, epithelial-mesenchymal transition (EMT), and fibrotic progression [13].

Intercellular mechanical signaling is equally critical. Cadherin-mediated junctions and cadherin switching during EMT contribute to fibrotic remodeling [14]. Moreover, Piezo1 has emerged as a key sensor in matrix metalloproteinase (MMP) 13-positive fibroblasts, activating a Ca^{2+}-hypoxia-inducible factor alpha (HIF-1α)-vascular endothelial growth factor (VEGF)-MMP13 cascade that promotes fibroblast migration and ECM deposition [15].

A brief introduction to the Piezo family

Mechanosensitive cation channels serve as essential mediators that convert mechanical stimuli into electrochemical signals [16]. Among them, Piezo1 and Piezo2, first identified by Ardem Patapoutian and colleagues, represent a distinct family encoded by Fam38a and Fam38b, respectively [17].

Structurally, Piezo1 assembles into a unique trimeric, propeller-shaped complex, with each subunit comprising ~38 transmembrane helices, forming peripheral blades that curve to create a dome-like architecture in the resting state [18–20]. High-resolution cryo-EM studies have identified key domains, including a central extracellular cap overlying the ion-conducting pore and an intracellular beam-like structure that acts as a lever during mechanical stimulation [18–21]. The overall architecture resembles a bowl-shaped structure with a central indentation projecting toward the cytoplasmic side. This structural configuration enables Piezo1 to sense mechanical forces conveyed through the lipid bilayer, cytoskeletal tension, or ECM [22]. The peripheral end of the beam flattens downward upon membrane stretch, acting as a lever to lift the central cap region and facilitate opening of the ion-conducting pore [20]. Upon activation, Piezo1 permits the influx of cations, predominantly Ca^{2+}, but also Na^{+}, K^{+}, and Mg^{2+}, whereas Piezo2 exhibits broader cation permeability [17]. Cation influx in turn initiates downstream signaling pathways such as p38-mitogen-activated protein kinase (MAPK) and YAP/TAZ, linking mechanical stimuli to gene expression, inflammation, and fibrotic remodeling.

Functionally, Piezo1 is mainly expressed in non-sensory tissues subjected to fluid shear or pressure, where it contributes to vascular development [23], red blood cell volume regulation [24], epithelial homeostasis [25], and lineage specification in neural and urinary systems [26, 27]. In contrast, Piezo2 is primarily found in sensory neurons and Merkel cells, mediating mechanosensory processes such as touch [28], proprioception [29], nociception [30], and functions in hearing [31], gastrointestinal, and respiratory physiology [29, 32].

In recent years, Piezo1 has emerged as a pivotal mechanosensitive ion channel, attracting increasing attention for its roles in diverse physiological and pathological processes. Given the well-established link between fibrosis and mechanical stress, as discussed above, Piezo1 has been implicated as a central mediator in fibrotic progression. Studies have shown that its activation contributes to fibroblast contractility and matrix deposition in multiple tissues. For instance, in skin fibrosis, Piezo1 promotes a wingless/integrated (Wnt) 2/Wnt11-C-C motif chemokine ligand (CCL) 24-driven positive feedback loop that sustains fibrotic signaling [33]; similarly, its profibrotic functions have been reported in kidney, lung, and cardiac models [22, 34].

Despite these findings, no comprehensive review has yet summarized Piezo1's mechanistic roles across organ systems in fibrosis. Besides, given the systemic burden of fibrosis across diseases [35], and the limitations of current therapies, elucidating how mechanical forces orchestrate fibrotic responses offers a promising avenue for targeted therapeutic innovation. Therefore, a focused discussion is warranted to consolidate current knowledge and explore Piezo1 as a potential therapeutic target in fibrotic diseases.

Purpose of this review

Piezo1 is broadly expressed across multiple organs and has been increasingly implicated in the pathogenesis of tissue fibrosis. However, despite growing evidence, systematic reviews integrating its roles across different fibrotic contexts remain scarce. This prompted our effort to synthesize current insights into Piezo1's functions in fibrosis. As a mechanosensor closely linked to fibroblast activation and ECM remodeling, Piezo1 emerges as a compelling therapeutic target.

Nonetheless, translating these findings into clinical strategies remains challenging. The structural complexity of Piezo1, including its conformational dynamics and downstream signaling, offers only preliminary guidance for drug development. Moreover, fibrosis manifests uniquely across tissues, underscoring the need to clarify both shared and context-specific roles of Piezo1.

In this review, we outline Piezo1's contributions to fibrotic progression across organs, evaluate its potential as an anti-fibrotic target, and examine current applications of Piezo1 modulators in preclinical models. We aim to inspire further research into Piezo1-targeted therapies and deepen mechanistic understanding to support future clinical translation.

Review

Piezo1 in tissue fibrosis

Integumentary system

Skin fibrosis. In recent years, Piezo1 has emerged as a key mechanosensitive molecule in the regulation of skin fibrosis.

It not only senses ECM stiffness and mechanical tension to activate fibroblasts but also interact with various signaling pathways, such as Ca^{2+}-myosin light chain kinase (MLCK), extracellular regulated protein kinases (ERK)/AKT, and Wnt/CCL4, and engages in amino acid metabolic circuits, forming positive feedback loops that sustain fibrotic progression. This section systematically reviews the regulatory roles of Piezo1 in skin fibrosis across four dimensions: fibroblast activation, metabolic modulation, immune involvement, and tissue remodeling, highlighting its therapeutic potential.

Piezo1: key mechanoresponsive targets in fibroblast activation

After skin injury, fibroblasts are regulated by various cytokines and changes in the microenvironment. These cells become activated and differentiate into myofibroblasts, undergoing phenotypic changes such as elongation of cell shape and upregulation of fibrosis-associated proteins, including α-smooth muscle actin (α-SMA) and platelet-derived growth factor receptor-β [36]. Activated myofibroblasts secrete ECM components and cytokines, which in turn stimulate neighboring fibroblasts, mediate ECM remodeling, and promote fibrotic progression [37].

While cytokines have traditionally been viewed as key mediators of fibroblast activation, a 2020 study highlighted the indispensable role of para-tensile signals, mechanical tension perceived by cells, in this process [35]. Cytokine signaling alone is insufficient to sustain fibroblast activation; mechanosensation is also required to trigger and maintain this phenotype [35]. Intracellular pathways implicated in this mechanotransduction include the Piezo1-Ca^{2+}-MLCK axis and the discoidin domain receptor tyrosine kinase 2 (DDR2)/integrin-focal adhesion kinase (FAK)-phosphoinositide 3-kinase (PI3K)/AKT-actin-related proteins-2/3 (ARP2/3) cascade, both of which regulate actin dynamics and drive downstream fibrogenic gene expression [35]. Furthermore, differential mechanical tension between fibrotic and normal tissues generates para-tensile forces at the interface, thereby activating fibroblasts in the boundary zone and propagating fibrosis into adjacent regions [35].

In parallel with fibroblast mechanotransduction, emerging evidence suggests that macrophage-to-myofibroblast transition (MMT) also contributes to fibrotic progression. A recent study demonstrated that MMT may generate $CD74^{+}$ fibroblasts in keloid tissues, which sense increased substrate stiffness and activate Piezo1 [38]. This mechanosensitive activation facilitates Ca^{2+} influx, triggers downstream ERK1/2 and AKT signaling cascades, and enhances fibroblast proliferation and migration [38].

Building on this, a 2024 study identified a novel intracellular circuit—the Piezo1–Wnt2/Wnt11-CCL4 axis—as a key driver of fibroblast activation and matrix remodeling [33]. This axis establishes a positive feedback loop [39] whereby increased matrix stiffness activates Piezo1, promoting myofibroblast differentiation and secretion of ECM proteins. These matrix components in turn reinforce tissue stiffness, thereby amplifying fibroblast activation and sustaining fibrotic expansion.

Piezo1-amino acid metabolic crosstalk in fibroblasts

In addition to fibroblasts activation, the regulation of cellular metabolism plays a pivotal role in scar formation. Metabolic reprogramming in fibroblasts, particularly shifts in fatty acid oxidation and glycolysis, directly influences the synthesis and degradation of ECM components [40]. A recent study revealed that dermal fibroblasts in mice utilize Piezo1 to sense ECM stiffness and transduce this mechanical cue into metabolic signals. This mechanotransduction cascade upregulates ornithine aminotransferase (OAT), arginase-1 (Arg1), and the mechanosensitive kindlin-2-pyrroline-5-carboxylate reductase 1 (PYCR1), while downregulating proline dehydrogenase (PRODH), thereby enhancing arginine and proline metabolism [41]. These metabolic shifts promote ECM biosynthesis and contribute to fibrotic progression. Functionally, Piezo1 deletion markedly reduces OAT, Arg1, and PYCR1 expression, while restoring PRODH levels, underscoring Piezo1's regulatory role in fibroblast metabolism [41].

Mechanical cues drive hypertrophic scarring formation

Hypertrophic scarring (HS) is a proliferative skin disorder that typically arises at sites of trauma such as papules, incisions, and burns, and is characterized by excessive collagen deposition that results in raised, thickened scars [42]. Recent studies have identified elevated Piezo1 expression in both human and rat HS tissues, with prominent localization in myofibroblasts [43]. During HS formation, fibroblasts sense mechanical stimuli via Piezo1, which promotes their phenotypic transformation into a fibrotic, highly proliferative state and enhances cell migration and proliferation [44, 45]. This mechanosensitive response is likely mediated by increased intracellular Ca^{2+} influx through Piezo1 channels [43].

Piezo1 acts as a molecular brake in skin repair by modulating inflammatory responses

Inflammation represents the initial stage of skin wound healing, and its delay can lead to increased scarring [46]. During wound repair, Piezo1 can regulate the inflammatory response during skin wound healing. When the peripheral environment undergoes changes in stiffness, such as the implantation of hard objects or the presence of preexisting fibrotic scars, Piezo1 can mediate macrophage Ca^{2+} influx, polarize macrophages and activate downstream nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), eventually enhancing the inflammatory response and slowing wound healing [47].

Consistent with these results, research by Will Wood et al. suggested that knocking out Piezo in *Drosophila* embryos significantly accelerates wound healing. The cause is primarily due to the following: (i) the loss of Piezo accelerates the migration of wound-edge epidermal cells toward the wound; and (ii) the loss of Piezo disrupts calcium homeostasis in the inner epidermis, reducing injury-induced reactive oxygen species (ROS), decreasing the number of recruited immune cells, alleviating inflammation, and accelerating wound healing [48]. However, the cost of faster wound healing is the disruption of myosin filament alignment at the wound site, causing the healed wound to lose its elliptical shape and symmetry [48]. $Piezo^{-/-}$ embryos exhibit a significantly greater death rate in the early stages of development when they are injured [48]. Therefore, Piezo1 likely plays a 'braking' role in the wound healing process, promoting a 'slower but safer' manner of wound closure. Although there is no direct evidence of Piezo1-mediated regulation of inflammation and fibrosis, this direction is worth further exploration.

Therapeutic potential of Piezo1 in cosmetic dermatology and skin regeneration

As the demand for beauty grows continuously, skin fibrosis caused by filler materials is gradually attracting public

attention. Recent studies have found that poly-L-lactic acid (PLLA) may induce Piezo1 activation, leading to the upregulation of ERK1/2, AKT/mechanistic target of rapamycin (mTOR) and TGF-β signaling pathways by Ca^{2+} influx, enhancing fibroblasts proliferation and collagen synthesis [49].

Studies found that low-frequency ultrasound electrophoresis (LFS) can reduce the amount of collagen and scarring by reducing calcium influx, which is regulated by Piezo1 channels [50]. After the Piezo1 channel was knocked down, the effect of LFS on primary keloid fibroblasts significantly reduced, and the application of GsMTx-4 prevented LFS-induced migration inhibition; however, the mechanism of Piezo1 in this process is still unclear [50].

Diabetic foot. Under hyperglycemic conditions, diabetic wounds are prone to delayed healing and excessive scarring, primarily due to prolonged inflammation, microvascular dysfunction, and peripheral neuropathy [51–53]. Growing evidence suggests that Piezo1-mediated mechanotransduction contributes to these pathological dimensions.

Hyperglycemia induces the upregulation of Piezo1 across various hematopoietic lineages, including platelets, erythrocytes, and neutrophils, driven in part by clonal expansion of Piezo1-high hematopoietic stem cells and subsequent lineage remodeling in diabetes [54]. In platelets, elevated Piezo1 enhances shear stress sensitivity, promoting calcium influx and phosphatidylserine exposure [55, 56], two key mediators of procoagulant activity. In erythrocytes, Piezo1 overexpression facilitates adhesion to vascular walls [54, 57], while in neutrophils, it potentiates NETosis [54], collectively intensifying thrombotic risk.

In vascular endothelial cells, Piezo1 acts as a shear stress sensor that regulates vasomotor tone [58]. However, its expression is significantly reduced in diabetic patients, potentially contributing to microvascular dysfunction [59]. Meanwhile, Piezo2 expression is associated with neuropathic pain: elevated in patients with painful neuropathy but markedly diminished in those with painless forms [59].

Together, these findings position Piezo1 as a mechanobiological nexus linking systemic metabolic disturbance with immune dysfunction, vascular injury, and neuropathic remodeling in diabetic wound pathology.

Circulatory system

Cardiac fibrosis. Accumulating evidence highlights Piezo1 translates mechanical stress into pro-fibrotic signals, governing fibroblast activation, endothelial inflammation, and smooth muscle remodeling across cardiac chambers and valves. It promotes fibroblast activation, endothelial inflammation, and smooth muscle remodeling through Ca^{2+} influx and key signaling pathways such as MAPK and interleukin (IL)-6, contributing to structural stiffening and fibrotic progression.

Piezo1-mediated IL-6/MAPK Axis as a central pathway in cardiac fibroblast activation

Cardiac fibroblasts (CFs) are the most abundant non-myocyte cells in the heart [60]. Under physiological conditions, they remain quiescent [61]. However, upon cardiac injury or pathological stress, CFs become activated and differentiate into myofibroblasts, a process partially mediated by Piezo1 [62].

During ventricular overload, activated CFs promote interstitial fibrosis and cardiomyocyte hypertrophy, which initially serves to preserve structural integrity and prevent ventricular rupture [63]. Yet, in progressive heart disease, mechanical strain disrupts ECM integrity and releases profibrotic mediators such as TGF-β and damage-associated molecular patterns (DAMPs) [64]. These changes enhance Piezo1 mechanosensitivity in CFs [62, 65], upregulate its expression, and accelerate MF differentiation, establishing a self-amplifying loop of fibrosis [39, 66].

Two key phenomena intensify this loop:

1. Stress-induced Piezo1 translocation: under excessive strain, Piezo1 translocate from caveolae to the cardiomyocyte membrane, increasing its mechanical responsiveness [67].
2. Mitochondrial localization: In CFs, intracellular Piezo1 localizes to mitochondria, amplifying fibrotic signaling upon activation [62].

Mechanistically, Piezo1 activation triggers p38/MAPK signaling in CFs, upregulating IL-6 expression in a concentration-dependent manner [68]. Elevated IL-6 level correlates with cardiac fibrosis and hypertensions [69], while fibroblast-specific p38α signaling is a key driver of hypertrophic and fibrotic remodeling [70].

In parallel, Piezo1 activation in pulmonary artery smooth muscle cells induces Ca^{2+} influx, promoting hyperproliferation and elevating pulmonary vascular resistance [34], which secondarily exacerbate right ventricular hypertension and structural remodeling.

Maintenance of cardiac homeostasis by Piezo1

Piezo1 plays a critical role in maintaining normal cardiac function and development. Both its excessive activation and genetic deletion disrupt calcium homeostasis and ROS signaling, thereby promoting cardiac dysfunction and fibrosis [71].

In Piezo1-specific knockout mice, intermuscular fibrosis is significantly increased by 18 weeks of age [71]. On the other hand, overexpression of Piezo1 leads to dilated cardiomyopathy, accompanied by a comparable increase in intermuscular fibrosis [71]. Moreover, Piezo1 gain-of-function mutations result in the upregulation of hypertrophy-associated genes such as atrial natriuretic peptide, α-myosin heavy chain, and β-myosin heavy chain, along with elevated expression of fibrotic markers like collagen type III alpha 1 chain, reinforcing Piezo1's role in the pathogenesis of cardiac hypertrophy and fibrosis [72].

Piezo1 as a candidate mechanosensor in valvular fibrosis

Although direct evidence is limited, Piezo1 may contribute to valvular fibrosis through valve interstitial cells (VICs), a fibroblast subtype residing in the valve matrix. When activated, VICs differentiate into myofibroblasts or osteoblast-like cells, driving fibrosis or calcification [73].

Several ion channels regulate VIC activation and collagen secretion [74–77], though their mechanical sensitivity remains debated [78]. In contrast, Piezo1 likely functions as a direct mechanosensor in VICs, mediating Ca^{2+} influx and modulating transient receptor potential (TRP) channel activity [79], similar to its role in cardiac fibroblasts.

Mechanosensitive Piezo1 activation in atrial fibroblasts

A 2021 study confirmed that Piezo1 serves as a mechanosensor in human atrial fibroblasts. Upon mechanical stimulation, Piezo1 mediates Ca^{2+} influx, subsequently activates

calcium-sensitive potassium selective Ca^{2+}- activated large conductance potassium channel (BKCa) potassium channels [80]. This interaction highlights Piezo1 as the primary initiator of mechanotransduction in atrial fibroblasts, with BKCa channels acting downstream in this signaling cascade.

Vascular fibrosis. In addition to its role in cardiac fibrosis, Piezo1 contributes to vascular pathology by mediating endothelial and smooth muscle responses to mechanical stress. In atherosclerosis (AS), a chronic disease driven by endothelial dysfunction and sustained vascular inflammation [81].

Piezo1 senses oscillatory shear stress and amplifies inflammatory signaling. Inhibition of Piezo1 with GsMTx4 slows plaque progression and may even reverse lesions [82]. Quercetin, a selective Piezo1 blocker, also suppresses AS without affecting other calcium pathways [83], indicating Piezo1-specific involvement.

In AS models, Piezo1 and aquaporin-1 are both upregulated in vascular smooth muscle cells, leading to increased cell volume and decreased vascular wall compliance [84], which may further contribute to vascular stiffness and disease progression.

Bone marrow fibrosis. In fibrotic bone marrow diseases such as primary myelofibrosis (PMF), Piezo1 emerges as a mechanosensitive mediator linking ECM stiffness to megakaryocyte dysfunction and impaired hematopoiesis.

PMF is a clonal hematologic tumor characterized by the progressive accumulation of reticulin and collagen fibers, which stiffen the bone marrow microenvironment [85]. Piezo1 plays a crucial role in sensing these mechanical changes and transducing them into altered cellular behavior.

A 2024 study showed that Piezo1 expression is elevated in mature megakaryocytes (MKs) from PMF models, alongside reduced platelet production *in vitro* [85]. When mouse MKs were cultured on substrates of varying stiffness, Piezo1 levels increased under stiff conditions, suggesting a link between matrix hardness and Piezo1 upregulation [85]. Notably, treatment with the Piezo1 inhibitor GsMTx4 restored platelet output to levels comparable to healthy controls, indicating that Piezo1 may represent a viable therapeutic target in PMF [85].

Respiratory system

Lung fibrosis. Pulmonary fibrosis arises from the interplay of radiation, mechanical stress, and chronic inflammation, with Piezo1 as a central integrator. Through distinct pathways, including Piezo1-TGF-β positive feedback, Rho-associated kinase 1 (ROCK1)-mediated remodeling, and YAP/NF-κB-regulated inflammation, Piezo1 links mechanical and immune signals to epithelial injury, fibroblast activation, and airway remodeling. The following sections detail these mechanisms and their roles in lung injury progression.

Radiotherapy-triggered Piezo1-TGF-β positive feedback loop

Approximately 35% of patients with lung or breast cancer develop radiation-induced pulmonary injury (RIPI) following chest radiotherapy, which may progress to irreversible pulmonary fibrosis at later stages [86]. Alveolar type II epithelial (AT II) cells play a key role in RIPI by undergoing EMT after radiation damage. Studies have shown that Piezo1 is expressed in rat alveolar epithelial cells and is upregulated after irradiation, along with elevated expression of EMT markers and fibrosis-related proteins [87]. siRNA-mediated suppression of Piezo1 partially reverses the expression of these proteins [87]. Mechanistically, Piezo1 activation triggers Ca^{2+} influx, activates HIF-1α, and enhances downstream TGF-β expression. TGF-β, in turn, further upregulates Piezo1, establishing a positive feedback loop that persistently promotes pulmonary fibrogenesis [87].

Piezo1-ROCK1 and EMT drives mechanical stretch-induced airway remodeling

Mechanical stress from abnormal ventilatory states, such as altered spontaneous breathing [88] or mechanical ventilation (MV) [89–92], disrupts intrathoracic pressure and contributes to lung injury [93] and fibrosis [94]. Mechanical stretch activates Piezo1 in both lung epithelial cells and fibroblasts, leading to Ca^{2+} influx that drives EMT and ECM deposition [89, 95]. In epithelial cells, Ca^{2+}-induced extracellular ATP (eATP) release promotes EMT and fibrosis, reversible by eATP depletion [89]. In fibroblasts, stretch-triggered ERK signaling enhances ECM production [95]. Piezo1 knockout markedly reduces these fibrotic responses.

In airway smooth muscle cells (ASMCs), stretch reduces Piezo1 and integrin $\alpha V\beta 1$ expression [92], indicating increased motility and contributing to irreversible remodeling [94]. In acute respiratory distress syndrome (ARDS), resistance to spontaneous breathing exacerbates injury, correlating with reduced Piezo1 expression [88]. In AT II cells, Piezo1 activation by pathological stretch leads to Ca^{2+} influx, subsequently induces B-cell lymphoma-2 (Bcl-2) suppression, caspase-3 activation, and VE-cadherin degradation, disrupting cell adhesion [91, 96]. Additionally, Piezo1-induced activation of A disintegrin and metalloproteinase (ADAM) 10/17 promotes amphiregulin and junctional adhesion molecule A (JAM-A) release, exacerbating ARDS in the early stages and promoting EMT and pulmonary fibrosis in the late stage [97]. Through the Ras homolog family member A (RHOA)/ROCK1 axis, Piezo1 further disrupts vascular integrity and promotes ASMC migration, collectively advancing pulmonary leakage and progressive airway remodeling [90, 92].

Piezo1-YAP/NF-κB axis links chronic airway inflammation to pulmonary fibrosis

Beyond mechanical stretch, chronic inflammation also contributes significantly to airway remodeling and pulmonary fibrosis through Piezo1-mediated signaling. Asthma is marked by variable airflow limitation and airway hyperresponsiveness (AHR) [98, 99], with ASMCs undergoing hypertrophy in severe cases. This hypertrophy increases cellular sensitivity to mechanical stimuli and membrane tension, a process likely regulated by a Piezo1-YAP autoregulatory loop [98]. In group 2 innate lymphoid cells (ILC2s), which drive airway inflammation via cytokine secretion and eosinophil recruitment, Piezo1 inhibition enhances pro-inflammatory activity and exacerbates AHR [100, 101]. Conversely, activation of Piezo1 by Yoda1 suppresses ILC2 function. Mechanistically, Piezo1 induces KLF2 expression, which downregulates NF-κB and p65, thereby limiting ILC2 proliferation and cytokine release [99].

Nasal polyp fibrosis. Chronic rhinosinusitis is a persistent inflammation of the nasal and paranasal sinuses, often accompanied by nasal polyps (NPs), a condition involving EMT. A recent study revealed that Piezo1 participates in the EMT process in NPs. In an EMT model treated with Yoda1, Piezo1

activation increased the expression of vimentin and α-SMA while reducing E-cadherin levels, indicating an exacerbation of EMT [102]. Conversely, treatment with the non-specific Piezo1 inhibitor ruthenium red attenuated EMT by upregulating E-cadherin and downregulating vimentin and α-SMA [102].

Urinary system

Kidney fibrosis. Renal fibrosis arises from dynamic interactions between epithelial, stromal, and immune components under mechanical and inflammatory stress. Piezo1 functions as a central mechanosensor in this context, translating extracellular stiffness and fluid shear forces into intracellular signaling events. By activating pathways such as MAPK-YAP, Ca^{2+}/calpain, and CC chemokine receptor 2 (CCR2)-Notch, Piezo1 regulates epithelial plasticity, fibroblast activation, and macrophage polarization, thereby driving fibrosis across multiple renal compartments.

MAPK-YAP axis: basis of Piezo1-mediated ECM remodeling

ECM stiffness contributes to renal fibrosis by enhancing ECM production and collagen deposition, forming a self-perpetuating fibrotic loop [103]. This process is mediated by Piezo1, which senses changes in ECM stiffness and activates the MAPK pathway in renal mesangial cells, leading to phosphorylation of p38, c-Jun N-terminal kinase (JNK), and ERK. Subsequent YAP activation and nuclear translocation drive profibrogenic gene expression [104]. Piezo1 also promotes fibrosis by inducing apoptosis and mitochondrial dysfunction via the Bcl-2 associated X protein (Bax)/caspase-3 pathway [105]. Inhibition of Piezo1 or downstream effectors (MEK1/2, JNK, p38, YAP, or Bax) significantly mitigates fibrosis in obstructive nephropathy models [104].

Additionally, ureteral obstruction upregulates Piezo1 in urothelial cells in response to increased intraluminal pressure, wall shear stress, and disturbed urine flow [106]. This upregulation compensates for impaired peristalsis by enhancing Cajal pacemaker cell activity and boosting ureteral smooth muscle contraction, thereby aiding urinary flow and muscle cell tension restoration [106].

Microenvironmental mechanosensing promotes fibrosis and tumor progression

ECM in the tumor microenvironment of renal cell carcinoma serves not only as structural support, but also as a source of mechanical cues. In kidney renal clear cell carcinoma (KIRC), Piezo1 is activated by increased ECM stiffness, initiating the Ca^{2+}/calpain/YAP signaling cascade that drives tumor cell proliferation, migration, and invasion [107].

Similarly, in the renal collecting ducts, ECM stiffening upregulates and activates Piezo1, promoting the transcription of fibrotic markers such as TGF-β1, α-SMA, and fibronectin [108]. This process is mediated by Piezo1-induced calcium influx and subsequent activation of calpain-2, which cleaves talin-1 and enhances integrin β1 abundance, leading to downstream FAK activation [108, 109]. The fibrotic effects can be attenuated by the non-specific Piezo1 inhibitor GsMTx4 [108].

Piezo1-mediated macrophage polarization shapes renal fibrosis via CCR2 and notch signaling

Emerging evidence suggests that Piezo1 in renal macrophages plays a pivotal role in modulating fibrosis progression [110]. Macrophages exhibit functional plasticity in fibrotic kidneys [111, 112], polarizing into pro-fibrotic M1 or anti-fibrotic M2 phenotypes [113]. Myeloid-specific Piezo1 knockout in mice significantly attenuates folic acid-induced renal fibrosis [110]. This knockout reduces CCR2 surface expression on macrophages, diminishing their responsiveness to CCL2 and impairing Notch signaling activation, both of which contribute to reduced macrophage infiltration [110]. Furthermore, the absence of Piezo1 disrupts the activation of both M1 and M2 subsets, impairs inflammatory responses, and inhibits EMT, collectively suppressing renal fibrogenesis [110].

Bladder fibrosis. Bladder outlet obstruction (BOO), frequently caused by benign prostatic hyperplasia (BPH), leads to chronic mechanical overload that promotes progressive and irreversible bladder fibrosis [114, 115]. This fibrotic remodeling is characterized by excessive ECM deposition, tissue stiffening, and myofibroblast activation. Recent studies highlight Piezo1 as a central mechanosensor in this context, coordinating cell traction forces and mechanical signaling to drive fibrosis progression.

One hallmark of BOO-induced fibrosis is fibroblast-to-myofibroblast transition (FMT), originally attributed to non-muscle myosin IIA (NMIIA)-mediated contractility. However, transcriptomic and protein analyses from BOO and BPH models reveal that Piezo1 expression increases in parallel with fibrosis severity [116]. Notably, NMIIA and Piezo1 exhibit functional crosstalk, as NMIIA inhibition downregulates Piezo1, suggesting upstream regulation.

Mechanistically, Piezo1 senses matrix stiffening and transduces mechanical signals via the FAK/RHOA/ROCK pathway, which is attenuated by Piezo1 knockdown [117, 118]. In addition, high hydrostatic pressure caused by BOO activates Piezo1, triggering YAP1 and ROCK1 signaling to upregulate profibrotic factors in bladder fibroblasts [119]. These molecular events converge to sustain FMT and ECM production, reinforcing the fibrotic loop [116].

Functionally, Piezo1 knockdown reverses ECM accumulation and improves bladder function, as evidenced by reduced voiding pressure and normalized voiding intervals. Comparable effects are observed with GsMTx4 [116]. These findings establish Piezo1 not only as a key mechanosensor in BOO-induced bladder fibrosis, but also as a promising therapeutic target for reversing pathological remodeling.

Gastrointestinal system

Oral submucosa fibrosis. Oral submucous fibrosis (OSF) is a chronic progressive disorder of the oral mucosa, characterized by epithelial atrophy and ECM stiffening [120]. Compared with normal tissues, OSF epithelium exhibits decreased E-cadherin and increased vimentin expression, suggesting EMT as a key process in disease progression and potential malignant transformation. ECM stiffening in OSF activates Piezo1, which promotes epithelial cell proliferation and EMT [121]. Mechanistically, Piezo1 upregulates YAP and vimentin at both mRNA and protein levels, enhances YAP nuclear translocation, and further suppresses E-cadherin expression, reinforcing the EMT process [121].

Liver fibrosis. The role of Piezo1 in liver fibrosis is complex and context-dependent, with evidence supporting both protective and pathogenic functions. These divergent effects appear to hinge on the degree of Piezo1 activation and the stage or severity of fibrosis.

In mild fibrotic states, Piezo1 exerts anti-fibrotic effects by promoting macrophage efferocytosis. Wang Yang's group demonstrated that myeloid-specific deletion of Piezo1 aggravates liver fibrosis due to impaired clearance of apoptotic neutrophils, a process normally facilitated by Piezo1 sensing cytoskeletal stiffening [122].

Conversely, in models of advanced liver fibrosis induced by high-dose and frequent tetrachloromethane administration, Piezo1 overexpression disrupts redox homeostasis. It leads to a decline in antioxidant defenses, such as glutathione, superoxide dismutase, and plasma glutathione peroxidase, resulting in ROS accumulation and activation of the Notch signaling pathway, thereby exacerbating fibrosis [123]. Lithospermic acid mitigates this effect by reducing Piezo1-mediated oxidative stress and suppressing Notch activation [123].

These findings underscore the bidirectional role of Piezo1 in liver fibrosis, suggesting that in early-stage disease, moderate Piezo1 activity supports macrophage-mediated resolution, whereas in advanced fibrosis, overactivation amplifies oxidative injury and fibrogenesis.

Pancreas fibrosis. Mechanical pressure is a key pathological factor in pancreatitis initiation and progression. Piezo1, as a mechanosensitive ion channel, plays a vital role by sensing pressure to trigger acute pancreatic injury and by sustaining fibrotic responses that aggravate chronic disease. The following sections outline its involvement in both inflammatory onset and fibrosis amplification.

Acute pancreatitis initiation via Piezo1 activation

External pressure, arising from surgical trauma, gallstones, or abdominal injury, can trigger pancreatitis due to the pancreas's high sensitivity to mechanical stress [124–126]. Piezo1 is expressed in pancreatic acinar cells, where it mediates pressure sensing [127]. Conditional deletion of Piezo1 in these cells significantly protects against pancreatitis, and intraperitoneal administration of the Piezo1 inhibitor GsMTx4 markedly alleviates disease severity in mice [127]. In contrast, direct activation of Piezo1 using Yoda1 increases pancreatic injury markers such as edema, serum amylase, and myeloperoxidase, confirming Piezo1 as a critical upstream effector [127].

Piezo1-driven fibrotic amplification in chronic pancreatitis

In chronic pancreatitis and pancreatic tumors, ductal narrowing and persistent inflammation elevate intraductal pressure, forming a self-reinforcing fibrotic loop [128]. In pancreatic fibrosis, pancreatic stellate cells (PSCs) play a major role. In their quiescent state, PSCs express low levels of ECM proteins, but upon activation—often triggered by Piezo1-mediated Ca^{2+} influx—they lose their perinuclear lipid droplets and transform into matrix-producing myofibroblasts that secrete collagen I and fibronectin [129].

Piezo1, the most highly expressed mechanosensor in PSCs, responds proportionally to pressure magnitude and duration, resulting in synthesis of type I collagen and fibronectin in PSCs [128]. This activation also activates transient receptor potential vanilloid 4 (TRPV4) channels via phospholipase A2-mediated lipid signaling cascade, where Piezo1 initiates transient Ca^{2+} entry, and TRPV4 sustains it, amplifying PSC activation [128]. Additionally, Piezo1 enhances PSC migration through intracellular myosin-dependent cytoskeletal rearrangement, further contributing to fibrosis and pressure buildup [130].

Interestingly, in the acidic tumor microenvironment of pancreatic ductal adenocarcinoma (PDAC), intracellular acidification suppresses Piezo1 activity, potentially limiting fibrosis and offering a modulating effect on tumor progression [130].

These findings establish Piezo1 as both a sensor and amplifier of pancreatic pressure. In acute settings, it initiates inflammation, while in chronic conditions, it perpetuates fibrosis through a vicious cycle of mechanotransduction and matrix remodeling.

Nervous system

Piezo1 functions as a key mechanosensor in the central nervous system, responding to alterations in matrix stiffness and roughness associated with neurodegenerative conditions, mechanical implants, and inflammation. In Alzheimer's disease (AD), Piezo1 activity is implicated in both tissue damage and protective immune responses, suggesting a context-dependent role. The following sections highlight its involvement in astrocyte activation, amyloid plaque clearance, electrode-induced fibrosis, and neuroinflammation.

Piezo1 activation in Alzheimer's disease: β-amyloid accumulation as the central mechanism

Quiescent astrocytes are reprogrammed into reactive forms in response to various stimuli, including infection and injury [131]. In AD, Piezo1 is upregulated in reactive astrocytes surrounded by amyloid plaques, and shows specific reactivity to β-amyloid (Aβ) [132]. Neurons sense the increased nanoroughness caused by plaque accumulation via Piezo1, leading to neuronal apoptosis and morphological changes in astrocytes [133]. Similarly, tissue stiffening after neural injury activates Piezo1 in Schwann cells, impairing their proliferation and migration, thereby hindering neural repair [134]. This mechanotransduction promotes fibrous protein deposition in the AD brain. Inhibition of Piezo1 with GsMTx4 blocks these mechanosensory responses, mitigating the associated neurodegeneration [133].

Contrasting findings reveal that Piezo1 also mediates beneficial effects in AD. It senses the rigidity of Aβ fibrils, inducing Ca^{2+} influx in microglia, which enhances Aβ aggregation and phagocytosis, thereby compacting plaques and limiting neurotoxicity [135]. A lack of Piezo1 in microglia exacerbates Aβ pathology and cognitive decline, whereas activation of Piezo1 reduces the Aβ burden in the brain and cognitive impairment in mice [135]. These results suggest that Piezo1 plays divergent roles depending on cellular context and disease stage.

Coordination of TRPA1 and Piezo1 in fibrotic response to neural implants

Implanted neural electrodes often provoke chronic glial scarring and fibrosis [136], and Piezo1 has been identified as a key contributor to this response [137]. The interface between electrode and tissue are exposed to mechanical shear stress generated by respiration, blood flow, and movement [138, 139], and induces the expression of Piezo1 and transient receptor potential ankyrin 1 (TRPA1) [137]. These mechanosensitive ion channels are implicated in neuroglial proliferation and fibrotic capsule formation [137]. *In vitro* models simulating shear stress at the electrode interface suggest that Piezo1

promotes glial proliferation by enhancing ATP production and cellular metabolism [137].

LPS-induced Piezo1-NF-κB Axis in neuroinflammation modulation

Piezo1 also regulates neuroinflammatory signaling. At moderate concentrations (0.3–3 μM), Yoda1 suppresses inflammation by inhibiting NF-κB activity in glial cells, an effect that is reversed by GsMTx4 or Piezo1 silencing [140]. Similarly, Piezo1 inhibition enhances lipopolysaccharides (LPS)-induced cytokine secretion in microglia [141]. However, higher concentrations of Yoda1 (10 μM) promote the expression of IL-1β, IL-6, and TNF-α in LPS-stimulated BV2 microglia, suggesting a dose-dependent switch from anti-inflammatory to pro-inflammatory outcomes [142].

Collectively, these findings suggest that Piezo1 plays dual, context-dependent roles in the AD brain and neural fibrosis. It mediates injury-related mechanosensing, fibrotic tissue formation, and glial activation, yet also supports protective microglial functions under specific conditions. Differences in Piezo1 activation levels, cell types, and matrix mechanical states may explain the observed variability, underscoring the need for further mechanistic clarification to guide targeted interventions.

Comeraoculi

Maintaining intraocular pressure (IOP) relies on the balance of aqueous humor production and outflow. Recent studies suggest that Piezo1, a mechanosensitive ion channel, plays a dual role in regulating IOP and contributing to the development of presbyopia, highlighting its therapeutic potential in ocular diseases.

Aqueous humor typically drains through the trabecular meshwork (TM) [143], but fibrosis of TM cells impairs this outflow, leading to elevated IOP [144]. Piezo1 may counteract this fibrosis, offering promise for glaucoma treatment.

In vitro, Yoda1 inhibited the proliferation and migration of human TM cells in a dose-dependent manner [145]. Additionally, overactivation of Piezo1 also suppressed fibronectin expression by enhancing the arachidonic acid pathway and upregulating Prostaglandin F2α (PGF2α) and MMP2 expression [145, 146].

Further supporting its regulatory role, Piezo1 has been found to functionally interact with the mechanosensitive channel TRPV4. Piezo1 rapidly mediates ionic currents to buffer sudden IOP fluctuations, while TRPV4 provides a delayed stretch-activated current that contributes to longer-term regulation of TM outflow resistance [147]. Notably, Piezo1-derived metabolites can also serve as endogenous activators of TRPV4, suggesting a coupled mechanism of action [147].

In vivo studies reinforce these findings. In glaucoma model mice, Yoda1 administration significantly reduced IOP [145]. Conversely, elevated IOP itself can stretch TM cells, activating Piezo1 and triggering the JNK/p38 pathway, which induces TM cell ferroptosis [148]. Knocking down Piezo1 expression reverses this effect, suggesting a context-dependent role for Piezo1 in TM cell survival and fibrosis [148]. Together, these results indicate that Piezo1 may exert a dual function, both regulating TM cell behavior and mitigating fibrotic progression.

Beyond IOP regulation, Piezo1 also appears to contribute to the onset of presbyopia. In mice, application of Yoda1 eye drops increased the stiffness of the lens nucleus and cortex, and can be reversed by GsMTx4 [149]. This effect is linked to the upregulation of transglutaminase 2 following Piezo1 activation [149]. In presbyopia, similar mechanical stimuli from ciliary body contraction may activate Piezo1 and contribute to age-related lens stiffening [149]. These insights point to Piezo1 as a promising target not only for glaucoma, but also for the treatment of presbyopia.

Conserved mechanism features of Piezo1 across organs

Calcium signaling

Upon mechanical stimulation or Yoda1 activation, Piezo1 typically mediates calcium influx, initiating downstream signaling. In most tissues, this Ca^{2+} entry alone is sufficient to elicit pro-inflammatory, pro-migratory, or pro-apoptotic effects, thereby modulating the fibrotic phenotype (Figure 1, Table 1).

In the skin, Piezo1-induced Ca^{2+} influx promotes macrophage migration, proliferation, chemotaxis, and polarization toward an M1 phenotype. This inflammatory shift, partially driven by IL-6 and other cytokines, accelerates fibrosis [47, 49]. In alveolar epithelial cells, Piezo1-mediated Ca^{2+} triggers the TGF-β/Sma- and Mad-related protein (SMAD) cascade, upregulating ADAM10/17 and RHOA/ROCK1, which together induce EMT and apoptosis, advancing pulmonary fibrosis and injury [87, 89, 91, 97]. In renal tissues, Ca^{2+} influx activates calpain, further engaging p38 MAPK and YAP signaling to exacerbate fibrosis [104, 105, 108].

However, Piezo1 alone may not sustain long-term signaling, necessitating collaboration with other cation channels to reach an effective Ca^{2+} threshold. TRP channels, responsive to thermal, mechanical, and chemical cues, are common partners.

In VICs, Piezo1-induced Ca^{2+} fluctuations activate unidentified TRP channels, amplifying calcium signaling and cell responses [74]. Similarly, in pancreatic stellate and TM cells, TRPV4 is possibly activated by Piezo1-induced membrane depolarization or transient Ca^{2+} elevations [128, 147]. At neural implant interfaces, TRPA1 synergizes with Piezo1 to promote glial activation and scarring [137]. Notably, in TM cells, Piezo1 exhibits anti-fibrotic effects, contrasting its pro-fibrotic role elsewhere.

A unique case is seen in atrial fibroblasts, where Piezo1 activation secondarily engages BKCa channels. Though BKCa conducts K^+, its activation depends on localized Ca^{2+} niches, establishing an indirect amplification mechanism [80].

Evidence from multiple disease models, including hyperglycemic injury [140, 141], acute lung injury [89, 91], and renal fibrosis [105, 108], consistently shows that blocking calcium influx or chelating intracellular Ca^{2+} can mitigate Piezo1-mediated pathological effects. These findings emphasize the central role of calcium signaling as the initial trigger in Piezo1 pathway activation.

Piezo1-mediated calcium influx initiates key signaling cascades that define its dual fibrotic roles. As a critical upstream event, this Ca^{2+} entry governs downstream pro- or anti-fibrotic pathways, either independently or via crosstalk with other channels. Elucidating this calcium-dependent logic is essential for leveraging Piezo1 as a therapeutic target in organ fibrosis.

MAPK pathway

The MAPK pathway, a key regulator of cellular stress responses, proliferation, and migration, plays a central role in tissue fibrosis. Emerging evidence indicates that Piezo1-mediated mechanosensitive activation drives a conserved

Table 1. Piezo1 and tissue fibrosis (*in vivo*: ▲; *in vitro*: ■)

Organ	Cell type	Stimulation	Downstream pathway	Fibrotic phenotype	Ref.
Neural System	Neuron	Nanoroughness■	——	Fibrin deposition	[133]
	Microglia	Yoda1/Rigidity of Aβ plaques▲	Piezo1-Ca^{2+}-microglia aggregation and phagocytosis	Cognitive decline alleviation Aβ plaques compaction	[135]
		Yoda1■	NF-κB, TNF-α ↓ JNK1/mTOR phosphorylation ↓	Anti-inflammatory	[140, 141]
		Yoda1▲■	IL-1β, IL-6, TNF-α ↑	Pro-inflammatory cytokines secretion	[142]
	Neural glia	Milliscale fluid shear stress■	Piezo1/TRPA1 activation	Inflammatory response Formation of neural glial scars	[137]
	Schwann cell	Tissue rigidity■	TGF-β ↑	Inhibit proliferation and migration Impair neuronal repair	[134]
Kidney	Renal mesangial cell	Microenvironment stiffness▲■	MAPK-p38/JNK/ERK-YAP	ECM deposition	[104]
	Renal collecting tube cell	Mechanical stretch■	Ca^{2+}-calpain2-TGF-β	Renal fibrosis	[108]
		Yoda1▲■	Piezo1-Bax/Cytochrome-caspase-3	Cell apoptosis Renal fibrosis	[105]
	Macrophage	Yoda1/rigidity▲■	Piezo1-Ca^{2+}-calpain-cytokine Piezo1-Ca^{2+}-CCR2/Notch	Recruit bone marrow-derived macrophage Promote inflammation	[110]
	KIRC	Stiff matrix■	Piezo1-Ca^{2+}-Calpain-YAP translocation	KIRC growth and metastasis	[107]
Skin	Fibroblast	Fibroblast intercellular paratensile stimuli■	Piezo1-Ca^{2+}-MLCK pathway DDR2/intergrin-FAK-PI3K/AKT-ARP2/3 pathway	Actin assembling Fibrotic gene expression	[35]
		Stiff matrix■	Piezo1-arginine/proline metabolism ↑	ECM synthesis and fibrosis	[41]
		Stiff matrix■Bleomycin▲	Piezo1-Wnt2/Wnt11-CCL24	Fibroblasts activation ECM deposition	[38]
		Exposure to PLLA■	Piezo1-Ca^{2+}-ERK1/2-AKT Piezo1-TGF-β	Fibroblasts proliferation Collagen I/III synthesis	[49]
	Myofibroblast	Cyclic stretch■Early mechanical stretch of wound▲	Piezo1-Ca^{2+}-AKT Piezo1-Ca^{2+}-Bcl2	Fibroblasts proliferation and migration HS formation	[43, 44]
	Epidermis	Piezo1 KO in Drosophila embryo▲	Myosin cable heterogeneity Impair Ca^{2+}-ROS system	Inflammation inhibition Rapid but dysfunctional epidermal healing	[48]
	Macrophage	Stiff matrix■ Yoda1■▲	Piezo1-Ca^{2+}-Calpain-NF-κB-IFNγ	Polarization of macrophage Promote inflammation	[47]
Comeraoculi	Trabecular meshwork cell	Yoda1■	MMP2 ↑ Fibronectin ↓	Inhibit TM proliferation Reduce IOP	[145]
		Yoda1■	Piezo1-Ca^{2+}-TRPV4-Ca^{2+}-RHOA/eNOS	Cytoskeleton remodeling Increase IOP	[145, 147]
			Piezo1-PLA2-TRPV4	Inhibit fibronectin expression Reduce IOP	[146]
		Yoda1/cell stretching■	Piezo1-JNK/p38	TM cell ferroptosis	[148]

(*Continued*)

Table 1. Continued

Organ	Cell type	Stimulation	Downstream pathway	Fibrotic phenotype	Ref.
Lung	Alveolar type II epithelial cell	Irradiation■	Piezo1-HIF 1α-TGF-β-Piezo1	EMT mediated lung fibrosis	[87]
		MV in ARDS model■▲	Piezo1-Ca^{2+}-eATP	EMT mediated lung fibrosis	[89]
		Cyclic stretch■	Piezo1-Ca^{2+}-VE-cadherin degradation	Adhesive junction rupture Lung injury exacerbation	[91]
		Piezo1 knockdown■	Bcl-2 ↑	AT II cell apoptosis	[96]
		Yoda1/cell stretch■	Piezo1-ADAM10/17-JAM-A degradation	Reduction of cell contacts Cytokine secretion	[97]
	Airway smooth muscle cell	Cell volume expansion mediated membrane tension increase■	Piezo1-YAP auto-regulatory loop	Promote cell contraction	[98]
	ILC2	Yoda1■	Piezo1-KLF2-NF κB p65 ↓	Alleviate AHR and lung inflammation	[99]
	Lung fibroblast	Yoda1/Static and dynamic stretch■	Piezo1-Ca^{2+}-ERK	Increase ECM deposition Promotes airway remodeling	[95]
Cardio-vascular System	Cardiac fibroblast	Yoda1■▲ Gain-of-function mutation▲	Piezo1-Ca^{2+}-p38/MAPK-IL-6	Cardiac hypertrophy and fibrosis Ventricular remodeling	[68–70, 72, 150]
	Atrial fibroblast	Atrial fibrillation-induced mechanical force■	Piezo1-Ca^{2+}-BKCa	Cardiac fibrosis	[80]
	Myocardium Valve interstitial cell	Yoda1■▲	Piezo1-Ca^{2+} influx-Rac1-NOX2-ROS-Ca^{2+} spark	Intermuscular fibrosis Cardiomyopathy	[71]
		Mechanical stretch	Conjectural pathway: Piezo1-Ca^{2+}-TRP channel activation	Valve fibrosis and thickening	[73–76]
	Endothelial cell	Oscillatory shear stress■▲	Piezo1-Ca^{2+}/CaM/CaMKII-FAK/Src-YAP axis	Promote inflammation and atherosclerosis	[82]
		Quercetin■	Inhibit Piezo1-NF κB/NLRP3-IL 1β	Ameliorate inflammation and atherosclerosis	[83]
	VSMC	Yoda1/stiff matrix■	Piezo1/PKC/aquaporin-1 pathway	Increase VSMC volume Reduce aortic wall compliance	[84]
Pancreas	Pancreatic stellate cell	Yoda1/mechanical stretch■	Piezo1-Ca^{2+}—phospholipase A2-TRPV4-Ca^{2+}	Pancreas fibrosis	[128]
		Extracellular acidification■	Inhibit Piezo1-Ca^{2+}-myosin rearrangement	Alleviate pancreas fibrosis	[130]
	Pancreas acinar cell	Piezo1 specific KO▲/GsMTx4■	Hinder Ca^{2+} influx	Prevent pancreatitis	[127]
Bladder	Bladder fibroblast	BOO▲/stiff matrix■	NMIIA/Piezo1-FAK/RHOA/ROCK pathway	Bladder fibrosis\ Pro-inflammatory transition of macrophage	[116–118]
		High hydrostatic pressure■	Piezo-YAP1/ROCK1	Bladder fibrosis	[119]
Oral Mucosa	Epithelium	Stiff matrix■	Piezo1-YAP signaling	Proliferation of epithelial cells Oral fibrosis	[121]
Bone marrow	Megakaryocyte	Stiff matrix■	/	Promote primary myelofibrosis	[85]
Liver	Myeloid macrophage	Myeloid-specific Piezo1 deficiency▲	Inhibit Piezo1-Ca^{2+}—Rac1	Inhibit macrophage efferocytosis and transition to anti-inflammatory phenotype	[122]
		Lithospermic acid therapy/Piezo1 KO▲	Inhibit Piezo1-Ca^{2+}—Notch-mediated oxidative stress	Mitigate liver fibrosis	[123]
Nose	Bronchial epithelial cell	Yoda1▲	Vimentin and α-SMA ↑ E-cadherin ↓	Exacerbate EMT and NP progression	[102]

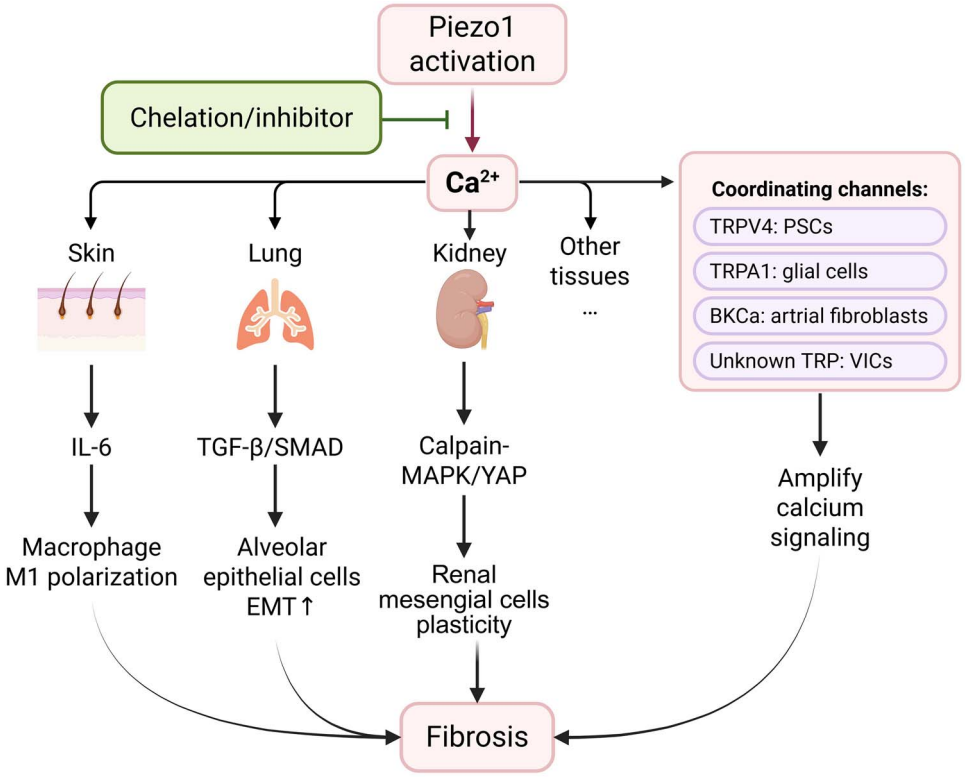


Figure 1. Piezo1-mediated Ca^{2+} influx and downstream fibrotic mechanisms across tissues. Piezo1 activation induces Ca^{2+} influx, triggering diverse profibrotic pathways across tissue-specific cell types. Key pathways include IL-6-mediated macrophage polarization in the skin, TGF-*β*/SMAD-driven epithelial-mesenchymal transition (EMT) in alveolar epithelial cells, and calpain-MAPK/YAP-mediated plasticity in renal mesangial cells. Coordination with other ion channels further modulate calcium signaling. Potential therapeutic targets such as Piezo1 inhibitor and Ca2+ chelator are indicated (created in BioRender. https://BioRender.com/vy0a5mi)

'mechanical force-signaling-fibrosis' axis via MAPK signaling, forming a core molecular basis for fibrosis across organs (Figure 2).

Organ-specific fibrotic responses are shaped by downstream Piezo1-MAPK pathway, with mechanosensitive inputs converging on context-dependent signaling circuits. In skin tissue, altered matrix stiffness or PLLA implantation triggers Piezo1-mediated calcium influx, leading to ERK1/2 activation and enhanced fibroblast migration and collagen synthesis, in cooperation with the AKT/mTOR pathway [49]. In the lungs, mechanical cues such as stretch or ventilation preferentially activate the Piezo1-ERK axis, driving excessive ECM deposition and fibrotic remodeling [95]. The heart exhibits a different signaling preference, where mechanical load predominantly engages the Piezo1-p38 MAPK pathway, resulting in fibroblast-derived IL-6 production and subsequent cardiac remodeling [68–70, 72, 150]. In the kidney, Piezo1 activation also converges on p38 MAPK, but further couples with YAP nuclear translocation to initiate pro-fibrotic transcriptional programs, underscoring its pivotal role in mesangial and interstitial fibrosis [104].

Thus, MAPK serves as a vital downstream effector of Piezo1, coordinating both conserved mechanotransduction and organ-specific fibrotic programs through its ERK and p38 branches. This duality illustrates how a single upstream sensor can integrate biomechanical cues into divergent fibrotic outcomes, offering insight into the modular logic underlying tissue remodeling across distinct microenvironments.

YAP/TAZ mechanotransduction

Piezo1 orchestrates tissue-specific fibrotic responses by engaging the YAP/TAZ pathway, serving as a central hub for mechanotransduction across diverse organ systems (Figure 3). In the kidney, it transduces matrix stiffness into p38 MAPK activation and YAP nuclear translocation, promoting mesangial activation and interstitial fibrosis [104]. This mechanosensitive cascade extends to renal carcinoma, where Piezo1 integrates ECM stiffening signals via a Ca^{2+}/Calpain/YAP axis, enhancing tumor cell invasiveness [107]. A similar self-amplifying loop in airway smooth muscle cells increases mechanical sensitivity and sustains myofibroblast-like activation [98]. In the bladder, Piezo1 activation during outlet obstruction upregulates YAP1 and profibrotic transcription [119]. Meanwhile, in oral epithelium, stiffness-induced Piezo1 signaling elevates YAP expression and drives nuclear translocation, suppressing E-cadherin and initiating EMT, thereby accelerating fibrotic remodeling in oral submucous fibrosis [121].

Together, these findings position the Piezo1-YAP/TAZ axis as a central integrator of mechanical stress and profibrotic signaling, linking force perception with gene regulatory networks across pathophysiological contexts.

Fibroblast activation

Fibroblasts are the most representative effector cells in multi-organ fibrosis, undertaking essential roles in ECM production, tissue remodeling, and mechanotransduction (Figure 4).

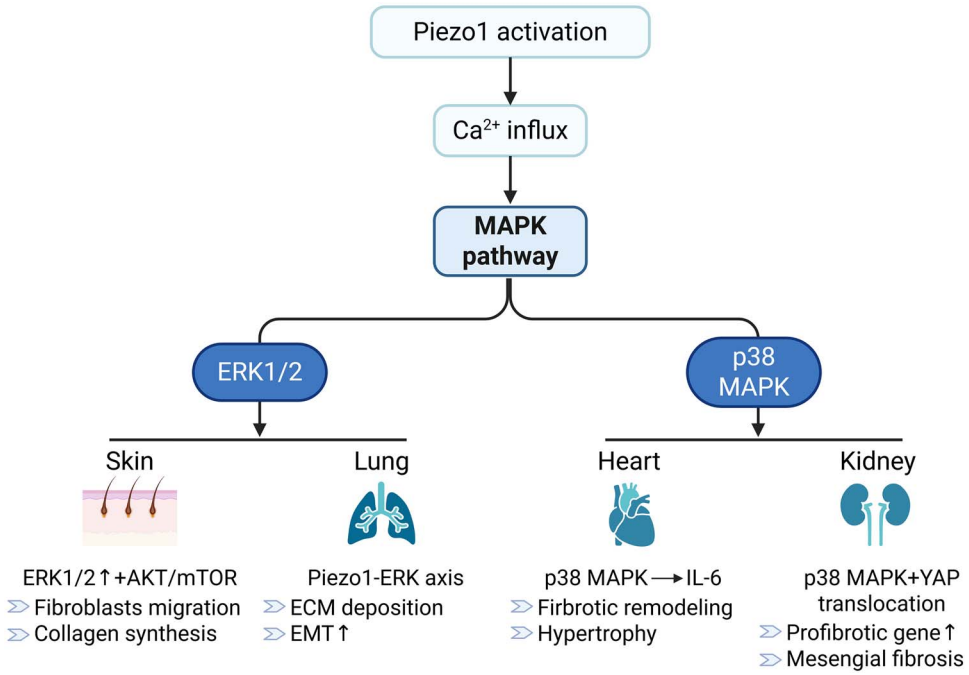


Figure 2. Piezo1-Ca^{2+}-MAPK axis driving profibrotic responses. Piezo1 activation triggers Ca^{2+} influx and therefore activates the MAPK signaling cascade (ERK1/2-p38-MAPK), leading to diverse profibrotic responses in tissue-specific contexts. Downstream effects include fibroblast migration and collagen synthesis in the skin, EMT and ECM deposition in the lung, fibrotic remodeling and hypertrophy in the heart, and profibrotic gene expression and mesangial fibrosis in the kidney (created by BioRender. https://BioRender.com/kjwcekd)

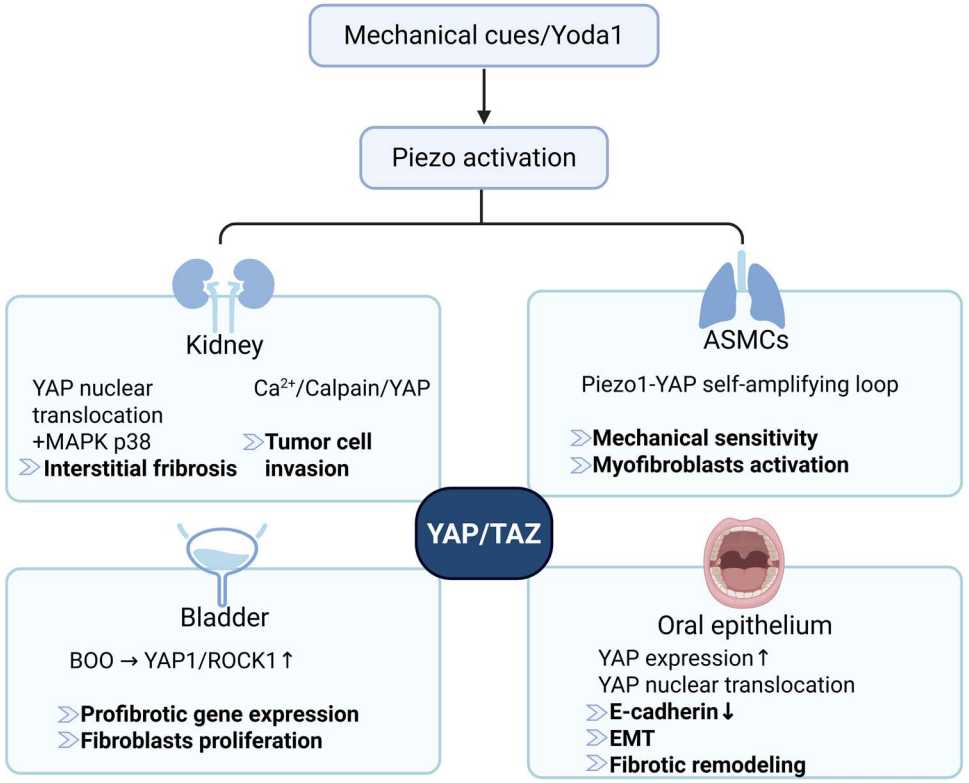


Figure 3. YAP translocation modulates Piezo1-mediated fibrosis in multiple tissues. Piezo1 activation triggers YAP nuclear translocation through Ca^{2+}-dependent and MAPK-related pathways, driving profibrotic responses in diverse tissues. YAP activation promotes fibroblast proliferation, extracellular matrix remodeling, and EMT, contributing to fibrotic progression in multiple organ systems. Representative mechanisms include YAP-p38 MAPK-mediated interstitial fibrosis in the kidney, YAP/ROCK1-driven fibroblast activation in the bladder, a self-amplifying Piezo1-YAP loop enhancing ASMC contractility and fibrosis, and YAP-induced EMT in oral epithelium (created by BioRender. https://BioRender.com/6rkphce)

Piezo1 is expressed in both quiescent fibroblasts and their precursor cells, and upon activation, it plays a pivotal role in directing cell fate transitions. In the skin, fibroblasts differentiate into myofibroblasts under the dual signaling of cytokine and para-tensile stimuli, resulting in excessive collagen deposition and tissue stiffening [35]. Additionally,

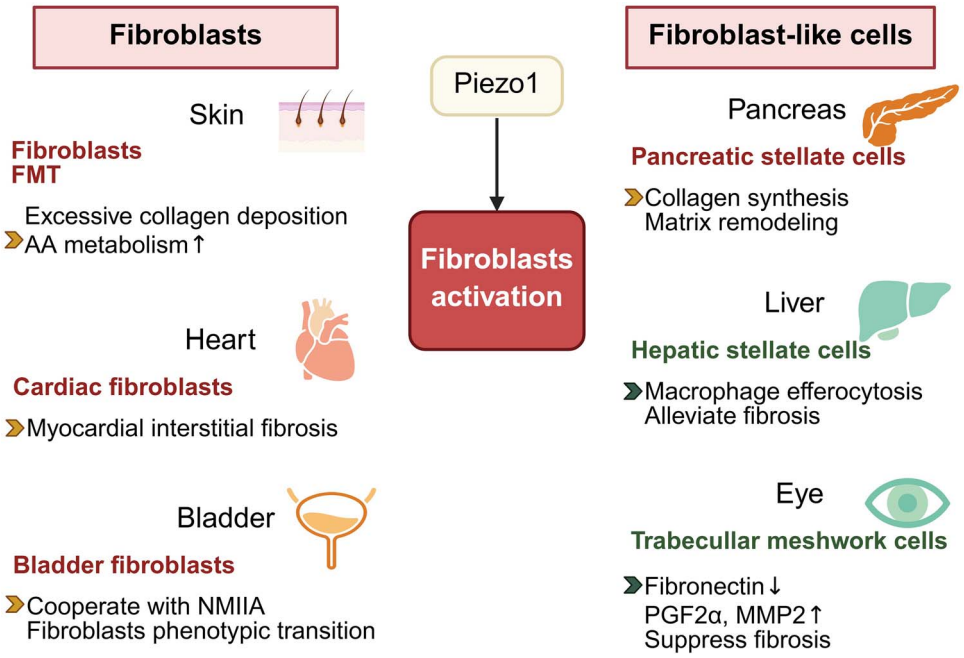


Figure 4. Context-dependent fibroblasts and fibroblast-like cells activation modulates tissue fibrosis. Activation of Piezo1 modulates fibroblast behavior and fibroblast-like cell functions in various tissues, contributing to either profibrotic or antifibrotic outcomes. Key mechanisms include promoting fibroblast activation and collagen deposition (skin, heart, pancreas), facilitating fibroblast phenotypic transitions and matrix remodeling (bladder, pancreas), thereby promoting fibrosis progression. While in HPCs and TM cells, their activation suppress fibrotic remodeling via macrophage efferocytosis and downregulation of fibronectin (created by BioRender. https://BioRender.com/rjlpkt9)

skin-resident macrophages can transdifferentiate into MFs within specific inflammatory microenvironments [8, 47]. Piezo1 not only modulates amino acid metabolism in dermal fibroblasts, enhancing their profibrotic phenotype [41], but also directly increases their mechanical sensitivity and promotes MF activation associated with hypertrophic scar formation [43].

In the heart, Piezo1 enhances fibroblast responsiveness to mechanical load, promoting differentiation into α-SMA-positive MFs and driving myocardial interstitial fibrosis [68]. In the bladder, Piezo1 collaborates with NMIIA to sense mechanical stress and facilitate fibroblast phenotypic transition [119]. Collectively, these findings underscore that in diverse organs, Piezo1 gives fibroblasts mechanosensitivity that promotes their progression toward fibrotic phenotype.

Meanwhile, although stellate cells originate from distinct lineages, they can acquire MF-like phenotypes and functions under pathological conditions. PSCs respond to local pressure changes via Piezo1-mediated calcium influx, which activates collagen synthesis and matrix remodeling, contributing significantly to pancreatic fibrosis [128]. Hepatic stellate cells (HSCs) Piezo1 has been shown to alleviate fibrosis indirectly by modulating hepatic macrophage efferocytosis [122], yet its expression in HSCs is also closely associated with their activation status, suggesting a potential direct role in promoting myofibroblast-like transitions.

TM cells also exhibit fibroblast-like responses to mechanical stress. While regulating aqueous humor outflow, they express Piezo1, which under physiological conditions promotes ECM turnover by suppressing fibronectin and activating PGF2α and MMP2 pathways [145]. Under glaucomatous pressure, however, prolonged Piezo1 activation can induce ferroptosis and tissue damage, indicating a context-dependent functional shift [148].

Across organs, fibroblasts act as both structural builders and mechanosensors, translating mechanical signals via Piezo1 into inflammatory, metabolic, and transcriptional programs that drive fibrosis. This positions them as key nodes for understanding and potentially modulating fibrotic remodeling.

Transforming growth factor β

TGF-β is a master regulator of fibrosis, driving EMT, fibroblast activation, and ECM deposition through both SMAD-dependent and noncanonical pathways. It also engages p38 MAPK, JNK, and PI3K/Akt to promote cytoskeletal remodeling and cell migration, reinforcing its central role across diverse fibrotic contexts (Figure 5) [9].

The Piezo1-TGF-β interaction drives fibrosis across tissues through conserved yet context-specific mechanisms. In skin, mechanical stiffening upregulates TGF-β via the Piezo1-Wnt2/Wnt11-CCL24 axis, forming a positive feedback loop [33]. In nasal polyps, TGF-β1 promotes EMT through Piezo1, aggravating mucosal remodeling [102]. Radiation-induced lung injury features mutual activation between TGF-β and Piezo1, accelerating fibrogenesis [87]. Similarly, in pancreatic stellate cells, Piezo1 transduces mechanical stress into TGF-β-driven fibrotic signaling [128]. This axis also contributes to CAF activation and matrix remodeling in tumors [9].

Mechanical stress-induced activation of Piezo1 upregulates TGF-β1 expression and promotes fibroblast activation and ECM synthesis via SMAD-dependent signaling. Conversely, TGF-β enhances both Piezo1 expression and mechanosensitivity, forming a self-amplifying loop that is particularly active under conditions of elevated matrix tension and cytoskeletal remodeling [33, 87, 102, 128]. This bidirectional coupling not only reinforces the persistence and irreversibility of fibrosis,

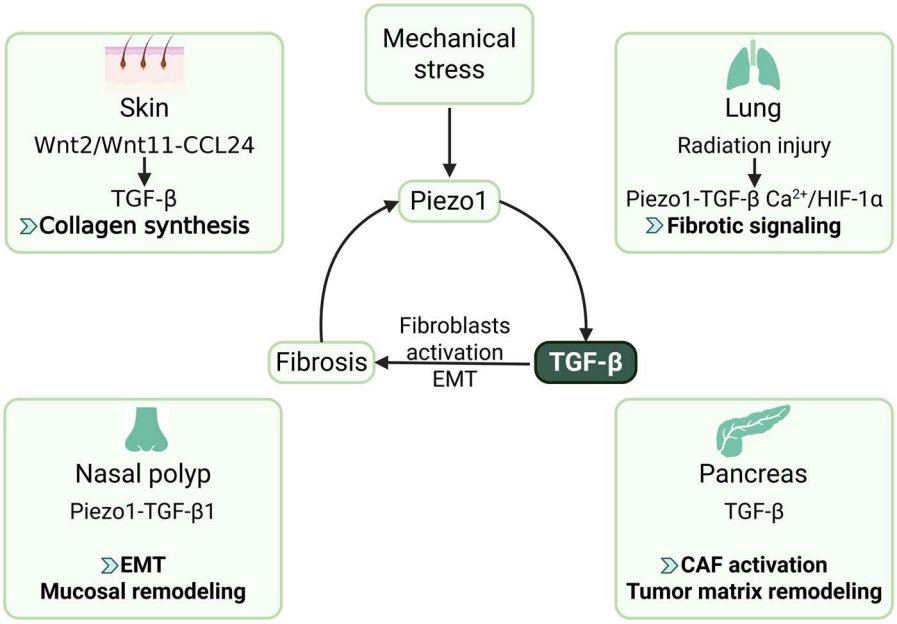


Figure 5. Piezo1-TGF-β forms a self-amplifying loop in tissue fibrosis. Mechanical activation of Piezo1 promotes TGF-β signaling, which coordinates diverse fibrotic and remodeling responses across tissues. These include Ca^{2+}/HIF-1α-mediated radiation-induced fibrosis in the lung, CAF activation and tumor matrix remodeling in the pancreas, EMT and mucosal remodeling in nasal polyps, and Wnt2/Wnt11-CCL24-driven collagen synthesis in the skin. Piezo1 and TGF-β mutually promote and activate one other, forming a pro-fibrotic feedback loop (created by BioRender. https://BioRender.com/xkfphln)

but also highlights the Piezo1-TGF-β axis as a promising cross-organ therapeutic target.

Modulators of Piezo1 activity

Piezo1 plays a key role in tissue fibrosis, making it an important target for both basic research and therapeutic development. Among its modulators, the small-molecule agonist Yoda1 and the peptide inhibitor GsMTx4 are the most widely studied, each with distinct mechanisms of action. In the following sections, we summarize these and other Piezo1-targeting compounds, focusing on their structure, pharmacodynamics, pharmacokinetics, and off-target effects (Table 2).

Agonists

Yoda1.

Pharmacodynamic characteristics

Yoda1 is the first synthetic small-molecule agonist identified to activate Piezo1 channels [151]. It lowers the mechanical activation threshold, delays channel inactivation, and can activate Piezo1 independently of mechanical stimuli, exhibiting typical allosteric agonist behavior [151]. In both cultured cells and reconstituted purified protein systems, Yoda1 shows consistent efficacy with an EC_{50} in the 10–50 μM range [152], while *in vivo* mouse and human Piezo1 with EC_{50} values of 17.1 μM and 26.6 μM respectively [151]. It has minimal effect on Piezo2, indicating high target selectivity. Structure–activity studies highlight the necessity of the 2,6-dichlorobenzyl and thioether groups for activity—loss of chlorines or oxidation of the thioether abolishes function [151]. Furthermore, its ability to activate purified Piezo1 in artificial lipid bilayers supports a direct binding mechanism [153].

Binding site analyses revealed that Yoda1 interacts with a narrow hydrophobic pocket near residues 1961 to 2063, involving alanine residues at positions 1718, 2091, and 2094 [153]. This site is located ~40 angstroms from the ion-conducting pore, suggesting an allosteric binding region [153]. Although Piezo2 contains a structurally similar pocket, sequence differences at key residues likely account for Yoda1's selective activation of Piezo1 [154]. Surface plasmon resonance and molecular dynamics studies confirm that Yoda1 binds to the Piezo1 fragment encompassing residues 1–2190, with a KD of 45.6 mM, indicating moderate binding affinity [155].

Pharmacokinetics characteristics

Pharmacokinetic data for Yoda1 remain limited. However, its derivative Yoda2, modified with a 4-benzoic acid group, exhibits significantly improved properties, including a lower *in vitro* EC_{50} of 1.14 mM and a microsomal half-life ranging from 24.6–29.6 minutes [156], representing a more than 20-fold increase in metabolic stability compared to Yoda1.

Specificity and off-target effect

Despite its favorable target specificity, low concentration of Yoda1 has been shown to inhibit the Kv1.3 potassium channel [157], which plays an important role in both innate and adaptive immunity, raising concerns about possible off-target immune effects. Further structural optimization may be required to improve selectivity and reduce unintended interactions.

Nonetheless, key pharmacokinetic attributes such as tissue distribution, organ accumulation, and blood–brain barrier permeability remain poorly characterized for Yoda1 and its analogs, limiting accurate assessment of their translational potential. In addition, the observed off-target raises concerns about immunological side effects.

Jedi1/2. Yanfeng Wang's group identified Jedi1 and Jedi2 as specific small-molecule activators of Piezo1 [155]. Both compounds share a 3-carboxymethylfuran scaffold, which

Table 2. A summary of Piezo1 modulators (*in vivo*: ▲; *in vitro*: ■)

	Activation mechanism	IC_{50}/EC_{50}	Effect Target	Off-Target	Ref
Agonist					
Yoda1	Reduce mechanical activation threshold; Delay Piezo1 inactivation	10–50 μM■▲	A narrow hydrophobic pocket in Piezo1's blade-like domain	Kv1.3	[151–153, 156, 157]
Jedi1/2	Lever mechanism induces Piezo1 opening	150–200 μM▲	Outer edge of Piezo1's blade-like domain	NA	[151, 155]
Local lipid environment	Maintain Piezo1 in a continuously activatable state	NA	Surrounding membrane	NA	[155, 158]
Inhibitor					
GsMTx4	Insert into the lipid bilayer to block the opening of mechanosensitive channels; Bind to extracellular domain of closed Piezo1	2 μM■	Extracellular domain of Piezo1; Surrounding membrane	Nav1.1–1.7 Kv11.1/11.2 Acetylcholine receptors	[160–167, 169, 170]
Streptomycin	Open-dependent inhibition	NA	Activated Piezo1	Ribosome	[171, 172]
Ruthenium Red and Gadolinium	Reversibly block the mechanically activated currents	5.4 ± 0.9 μM at -80 mV▲	E2495A, E2496A	Multiple cation channels	[166, 175, 203]
Lipid	Stiffen the plasma membrane; Alter membrane curvature	0.04mM■ (cholesterol)	Surrounding membrane	NA	[176–178, 180]
Aβ	Inhibit shear stress response by disrupting bilayer lipids	NA	Surrounding membrane	NA	[181, 182]
Urocortin 1	Probably via CRF-R1	NA	NA	NA	[183–185]
Antagonist					
Dooku1	Reversibly antagonize Yoda1's activating effect on Piezo	1.3–1.5 μM■	Same as Yoda1	NA	[186, 187]
Tubeimoside 1	Competitively antagonize Yoda1	6.97 μM■	NA	Potential hepatic toxicity	[188, 189]
Escin		NA			
Sal B	Antagonize Yoda1	NA	NA	NA	[190, 191]
Jatrorrhizine	Piezo1-dependent anti-inflammatory activity	NA	NA	NA	[199]

is believed to be essential for their activation of the channel. Unlike Yoda1, Jedi1 and Jedi2 do not share structural similarity with previously identified Piezo1 agonists [151], suggesting they engage Piezo1 through a distinct mechanism. Structural studies indicate that both Jedi and Yoda1 interact with sites located on the outer edge of Piezo1's blade-like domain and utilize the lever-like structural motif for activation [151]. However, the functional effects of these compounds differ significantly: Jedi-induced activation is characterized by rapid onset, transient signaling with notable decay, and high reversibility [155]. In contrast, Yoda1 induces a slower, sustained response with minimal signal decay and poor reversibility.

Sphingomyelinase and local lipid environment. In addition to exogenous agonists, endogenous lipid metabolism plays a key role in modulating Piezo1 function. Beech's group reported that sphingomyelin phosphodiesterase 3 reduces membrane sphingomyelin content, thereby increasing the pressure threshold for channel activation [158]. Conversely, the lipid product ceramide inhibits Piezo1 inactivation, maintaining the channel in a sensitized, activatable state [158]. This lipid-dependent gating modulation highlights the physiological relevance of membrane composition in Piezo1 regulation [155].

Together, these findings reveal that Piezo1 can be regulated by structurally unrelated small molecules and by dynamic changes in membrane lipid composition, pointing to multiple, mechanistically distinct pathways for tuning channel activity.

Inhibitors

GsMTx4.

Pharmacodynamic characteristics

GsMTx4 is a 35-amino acid amphipathic peptide [159] originally isolated from tarantula venom and remains the only known selective inhibitor of cationic mechanosensitive channels, including Piezo and TRP families [160–163].

It inhibits channel activity through two complementary mechanisms. One involves insertion into the lipid bilayer, where it alters membrane tension and reduces mechanical force transmission to the channel without directly engaging the gating structure [164]. This lipid-based mechanism also accounts for the activity of both L- and D-enantiomers, as it does not rely on stereospecific interactions [165]. The other mechanism targets the extracellular domain of the closed Piezo1 channel, preventing its activation when applied before mechanical stimulation, with near-complete inhibition observed [162]. The equilibrium binding constant Kd of GsMTx-4 to a lipid bilayer and IC_{50} for PIEZO1

are both ~2 μM [166]. Compared to conventional blockers like gadolinium, GsMTx4 shows higher specificity for mechanically gated cation channels, as demonstrated in rat motor reflex models.

Pharmacokinetics characteristics

Pharmacokinetic data suggest strong tissue retention. In ischemia/reperfusion models, a single injection of the D-enantiomer (GsMTx4-D) persisted in cardiac tissue for up to 8 days and significantly reduced infarct size, likely due to resistance to proteolytic degradation [167]. Although no direct data are available for oral or alternative routes, its peptide nature implies limited absorption and highlights the need for improved delivery strategies. GsMTx4 is reported to be non-immunogenic, biologically stable, and long-acting, with no direct interaction with mesenchymal stem cells with high Piezo1 expression [168].

Specificity and off-target effect

Despite its primary activity on Piezo1 (Kd $\approx$ 155 nM) and TRPC6, GsMTx4 also inhibits several voltage-gated ion channels, including Nav1.1–1.7 (IC_{50} ~7.4–14.1 μM), Kv11.1/11.2 (IC_{50} ~10.9–11 μM) [169], and acetylcholine receptors [170]. These off-target effects raise concerns for therapeutic use and underscore the need for improved selectivity.

While GsMTx4 shows promising membrane-targeting and pharmacological properties, comprehensive data on tissue distribution, systemic exposure, and long-term safety are still lacking. Future studies should address these gaps to better define its translational potential.

Streptomycin. Streptomycin is a hydrophilic aminoglycoside antibiotic previously reported as a non-specific inhibitor of mechanosensitive ion channels [162]. Unlike GsMTx4, which acts on closed channels, streptomycin inhibits only the activated state of Piezo1,referring to an 'open-dependent inhibition' [171]. Regarding pharmacokinetics, streptomycin is administered intramuscularly or intravenously, with a bioavailability of 84%–88% and an elimination half-life of 5–6 hours[172]. However, its lack of specificity and potential off-target effects on ribosomal function limit its therapeutic applicability for Piezo1-related interventions [172].

Ruthenium red and gadolinium. Ruthenium red and gadolinium are classical blockers of mechanosensitive polycation channels, including members of the TRP family [173, 174]. Studies have shown that both compounds can reversibly inhibit mechanically activated currents mediated by Piezo1 and Piezo2 in mouse models [17]. Ruthenium red acts as an open channel blocker on the extracellular side in a voltage-dependent manner, while gadolinium binds to phospholipids, compacting the membrane region surrounding the channel and preventing its opening [166, 175]. Both agents exhibit low specificity and can affect various cation channels, raising concerns about off-target effects.

Lipid. The mechanical sensitivity of ion channels like Piezo1 is influenced by the elastic properties of the lipid bilayer [176]. Saturated fatty acids, such as margaric acid, integrate into the plasma membrane, increasing membrane stiffness and thereby inhibiting Piezo1-mediated currents [177]. However, saturated fatty acids have a similar inhibitory effect on Piezo2 [178], suggesting a doubtful specificity.

In contrast, polyunsaturated fatty acids, including arachidonic acid and eicosapentaenoic acid, modulate Piezo1 inactivation kinetics by decreasing membrane stiffness [177]. These findings suggest that dietary fatty acids can fine-tune Piezo1 activity, although their systemic pharmacokinetics and potential off-target effects require further investigation.

In addition, cholesterol and other membrane lipids such as phosphatidylinositol 4,5-bisphosphate modulate Piezo1 activity by altering bilayer curvature, which affects its resting footprint and inhibits channel opening. *In vitro*, the IC50 of cholesterol in cultured cells is 0.04 mM [179].

β-amyloid. Amphiphilic molecules like Aβ peptides can modulate mechanosensitive channel activity by disrupting the organization of surrounding bilayer lipids [180, 181]. Both enantiomers of Aβ have been found to suppress Piezo1 responses to shear stress, suggesting that their inhibitory effect is likely mediated by membrane interaction rather than direct channel binding [182]. However, the precise mechanism and potential off-target effects of Aβ on other membrane proteins remain to be elucidated.

Urocortin 1. Urocortin-1 (Ucn1) is an endogenous peptide hormone with cytoprotective properties, particularly in response to mechanical trauma [183, 184]. It has been shown to inhibit load-induced intracellular calcium influx by blocking Piezo1 activity, while sparing TRPV4, resulting in a marked reduction in post-traumatic cartilage degeneration [185]. The protective effect is primarily mediated via the corticotropin-releasing factor receptor type 1 (CRF-R1), and has been observed with both pre- and post-impact administration [185]. However, the systemic pharmacokinetics of Ucn1 and its potential hormonal side effects necessitate further research to assess its viability as a therapeutic agent targeting Piezo1.

Antagonists of Piezo1

Dooku1. Dooku1, a structural analog of the Piezo1 agonist Yoda1, was designed through targeted modification of the pyrazine ring in Yoda1 [186]. Although Dooku1 lacks intrinsic agonistic activity and does not directly suppress basal Piezo1 channel function, it can reversibly antagonize Yoda1-induced activation of Piezo1 [186, 187]. Intriguingly, recent studies reveal that Dooku1 can induce a modest cation influx and elevate intracellular sodium levels in red blood cells, effects that are mitigated by the mechanosensitive ion channel inhibitor GsMTx4 [187]. These findings suggest that Notably, Dooku1 exhibits an IC_{50} of 1.3–1.5 μM in cultured HUVEC cells *in vitro* [186], whereas its inhibitory potency in red blood cells *in vivo* is approximately one order of magnitude lower, indicating context-dependent pharmacodynamics [187].

Natural product-derived Piezo1 antagonists. Several bioactive compounds derived from traditional Chinese medicine have emerged as promising Piezo1 antagonists, demonstrating both structural diversity and selective pharmacological activity. Notably, a group of triterpenoid saponins, including Tubeimoside I (TBMS1) and Escin, share the capacity to inhibit Yoda1-induced Piezo1 activation, largely in a concentration-dependent manner. TBMS1, extracted from Bolbostemma paniculatum, exhibits high efficacy *in vitro*

($IC_{50} \approx 6.97\ \mu M$) but is limited by poor oral bioavailability and potential hepatosplenic toxicity at elevated doses [188]. Escin, derived from *Aesculus hippocastanum*, also significantly reduces Piezo1-mediated calcium influx and pro-inflammatory signaling in endothelial cells, with diminished efficacy in Piezo1-deficient models, underscoring its channel-specific mechanism [189].

Salvianolic acid B (SalB), a phenolic compound derived from *Salvia miltiorrhiza*, exhibits potent inhibitory effects on Yoda1-induced Piezo1 activation [190]. In a murine model of atherosclerosis, SalB significantly attenuated plaque progression by inhibiting Piezo1 channel activity, suggesting intrinsic antagonistic potential [191]. Despite these promising vascular protective effects, its clinical translation is constrained by low systemic bioavailability [190].

In parallel, the protoberberine alkaloid Jatrorrhizine, from Coptis chinensis, exhibits Piezo1-dependent anti-inflammatory activity by attenuating endothelial responses in carotid ligation models, and is abolished in Piezo1-knockout conditions [192]. Collectively, these natural antagonists expand the chemical space of Piezo1 modulators and highlight the therapeutic potential of traditional medicinal compounds in targeting mechanosensitive ion channels.

Clinical potential and limitations of Piezo1 channel modulators

As a key mechanosensitive ion channel, Piezo1 plays a central role in various pathological conditions, including cardiovascular diseases, fibrosis, and degenerative cartilage disorders, making it an important therapeutic target. Currently, major modulators include membrane lipids, small-molecule agonists, inhibitory peptides, and endogenous regulators.

Cholesterol inhibits Piezo1 activation by increasing membrane stiffness, with an IC50 of 0.04 mM in cell-based assays [179]. Similarly, saturated fatty acids can alter membrane curvature and elevate the activation threshold of Piezo1 [177]. However, these effects rely on changes in membrane physical properties, lacking molecular specificity and potentially affecting other mechanosensitive channels such as TRPV4 [193].

Yoda1, the first identified small-molecule Piezo1 agonist, has been widely used in mechanistic studies [151]. GsMTx4, a peptide inhibitor derived from spider venom, effectively blocks Piezo1-mediated calcium influx [159]. Nevertheless, Yoda1's pharmacokinetic profile *in vivo* remains unclear [153]. While GsMTx4, as a small peptide, faces translational challenges due to its stability, delivery limitations and potential immunogenicity [162].

Urocortin 1 suppresses Piezo1 activity via the CRF-R1/cAMP/phospholipase A2 (PLA2) signaling axis and has been shown to protect chondrocytes from mechanical stress-induced injury [185]. Compared with other modulators, it operates through a more specific mechanism and originates from an endogenous regulatory pathway, offering greater physiological compatibility [185].

Several Piezo1 modulators have demonstrated preliminary therapeutic potential in murine models. For instance, GsMTx4 improves muscle function by blocking Piezo1 channels in a Duchenne muscular dystrophy mouse model, promoting muscle stem cell differentiation and reducing myofiber damage [194]. Moreover, Urocortin 1 has exhibited significant protective effects in injury-induced cartilage models [185].

Notably, targeted delivery strategies such as nanoparticles and liposomes can enhance drug accumulation in specific tissues, improving efficacy while minimizing systemic side effects. In an acute lung injury model, Piezo1-targeted aerosolized nanoparticles loaded with GsMTx4 enabled precise pulmonary delivery with promising results [195]. Similarly, an engineered nanodrug (CAQKERM@GsMTx4) achieved targeted delivery to hemorrhagic brain regions, promoting anti-inflammatory microglial polarization and reducing neuroinflammation [196]. Additionally, hendeca-arginine peptides (R11) have been shown to undergo macropinocytosis uptake in bladder cancer cells with hyperactivated Piezo1-integrin $\beta 1$ signaling [197], offering another potential strategy for tissue-selective delivery. The nervous system is a major site of glial fibrosis, but the blood–brain barrier (BBB) remains a key barrier to drug delivery. Strategies like magnetic nanoparticle-induced heating to transiently open the BBB may offer insights for delivering Piezo1 modulators [198]. These examples highlight the value of smart, Piezo1-guided delivery systems, which will be essential for translating Piezo1-targeted therapies into clinical practice.

A summary of Piezo1 in tissue fibrosis

This review focuses on the critical role of Piezo1 in fibrosis. Although its homolog Piezo2 was previously considered to play a minimal role in fibrotic processes, emerging evidence from the past year suggests otherwise. Recent studies have shown that Piezo2 also contributes to fibrotic remodeling in multiple tissues.

In idiopathic pulmonary fibrosis patients, Piezo2 expression is significantly upregulated [199]. In primary lung fibroblasts cultured on stiff substrates, Piezo2 knockdown markedly reduces α-SMA and collagen expression, indicating its involvement in fibroblast activation [199]. In cardiac fibroblasts stimulated with TGF-β, Piezo2 activation enhances autophagy and promotes fibrogenic responses through a mechanism involving YTH N6-methyladenosine RNA-binding protein 1-mediated m6A methylation of Piezo2 mRNA, which stabilizes its expression [200]. Similarly, in murine models of nephropathy, Piezo2 upregulation correlates with increased fibronectin deposition and TGF-β expression, supporting a potential profibrotic role in renal tissue [201, 202].

Together, these findings suggest that Piezo2 may act in parallel with Piezo1 in mediating mechanical stress-induced fibrosis. However, current research remains largely centered on Piezo2's expression dynamics and upstream regulation. Direct elucidation of its downstream signaling pathways is still lacking and represents an important area for future investigation.

Dual role of Piezo1 in tissue fibrosis

While Piezo2 has recently been implicated in fibrosis, Piezo1 remains a leading role in mechanotransduction. Its effects, however, are highly context-dependent, shaped by factors such as cell type, mechanical load, disease stage, and the local microenvironment. Understanding how these variables drive divergent downstream signaling is crucial to unraveling Piezo1's dual role in promoting or mitigating fibrosis across tissues (Table 3).

Table 3. Contextual factors influencing the bidirectional regulation of Piezo1

Regulatory Factor	Pro-Fibrotic Role	Anti-Fibrotic Role
Disease Stage	Late wound repair exhibits ROS overactivation leads to fibrosis [47]	Early wound repair maintains inflammation and healing stability [48]
	Sustained liver fibrosis constantly induces oxidative stress and exacerbates fibrosis [123]	Mild liver injury promotes macrophage efferocytosis [122]
	Intense amyloid stress drives gliosis [132–134]	Early neurodegeneration enhances amyloid elimination [135]
Cell Identity	Skin myofibroblasts sense matrix stiffness and promote ECM deposition [38]	Macrophage efferocytosis reduce liver fibrotic progression [122]
	Calcium influx in fibroblasts (skin, heart) activates YAP/TAZ, MAPK, TGF-β and promotes fibrosis [8, 33, 39, 43, 68]	Trabecular meshwork cell senses elevated IOP and promotes ECM degradation [146]
	Astrocytes sense amyloid stress and accelerate ECM deposition [132–134]	ILC2 suppress NF-κB and mitigates fibrosis and airway hperreactivity [99]
Mechanical Input	Sharp mechanical stimuli induce pancreatic stellate cells to synthesize fibronectin [128]	Low intensity mechanical cues restrict Piezo1 overactivation, therefore limiting fibrotic progression [122, 146]
	Excessive matrix stiffness enhances fibrotic cascades in skin and heart [33, 39, 68]	
Microenvironment	Neutral environment mediates pressure-induced Piezo1 activation and collagen synthesis in PSCs [128]	Acidic tumor microenvironment of PDAC suppresses Piezo1, therefore limiting fibrosis [130]
	Hypoxia coordinate with RIPI, activating HIF-1α and Piezo1, leading to sustained TGF-β signaling and fibrogenesis [87]	

Stage-specific roles of Piezo1 in injury and tissue remodeling

Piezo1's role in fibrosis varies with the stage of injury and tissue dynamics. During early wound repair, it senses matrix stiffening, activates NF-κB in macrophages, and prolongs inflammation, delaying closure in fibrotic or implanted tissues [47]. In contrast, its absence before injury reduces ROS and immune recruitment, accelerating but destabilizing healing [48].

A similar pattern is observed in liver fibrosis. Under mild injury, Piezo1 promotes macrophage efferocytosis and inflammation resolution, while its deletion worsens fibrosis [122]. As fibrosis progresses, such as sustained tetrachloromethane-induced liver fibrosis, however, persistent Piezo1 activation induces oxidative stress and Notch signaling, driving progression [123].

Likewise, in neurodegeneration, Piezo1 promotes gliosis and impairs repair in astrocytes and Schwann cells under mechanical or amyloid stress [132–134]. In contrast, Piezo1 in microglia enhances calcium-dependent amyloid clearance, its loss exacerbates plaque burden and cognitive decline, highlighting its protective role in early-stage pathology [135].

These findings highlight the stage-dependent nature of Piezo1, acting as either a fibrosis modulator or promoter depending on injury timing and cellular context.

Cell identity determines fibrotic directionality

The functional consequences of Piezo1 activation differ markedly across cell types. In immune cells such as macrophages and microglia, Piezo1 often plays a regulatory or protective role. In the kidney, myeloid-specific Piezo1 deletion reduces CCR2 expression and impairs Notch signaling, limiting macrophage recruitment, polarization, and EMT, thereby suppressing fibrosis [110]. Similarly, in mild liver fibrosis, Piezo1 facilitates macrophage efferocytosis by sensing cytoskeletal stiffening, and its loss exacerbates disease progression [122].

Non-classical immune-like cells exhibit similar effects. In trabecular meshwork cells, which share phagocytic and immunomodulatory traits with macrophages, Piezo1 activation reduces fibronectin and promotes ECM degradation via PGF2α and MMP2, alleviating ocular fibrosis [146]. In ILC2s, Piezo1 suppresses cytokine release by upregulating KLF2 and inhibiting NF-κB, mitigating airway hyperreactivity and fibrosis [99].

In contrast, Piezo1 activation in structural cells—fibroblasts, epithelial cells, and astrocytes—tends to be profibrotic. Fibroblasts increase ECM production and contractility through Piezo1-mediated calcium influx and downstream activation of YAP/TAZ, MAPK, and TGF-β pathways [8, 33, 39, 43, 68]. In cardiac fibroblasts, Piezo1 activation stimulates IL-6 secretion through p38 MAPK signaling [68] while in dermal and keloid fibroblasts, it contributes to matrix remodeling and scar formation under mechanical stress [33, 43, 50]. Astrocytic Piezo1, similarly, respond to mechanical or amyloid stimuli by promoting gliosis and matrix deposition [132–134]. Collectively, these patterns highlight a cell identity-dependent polarity in Piezo1's function.

Mechanical inputs shape functional outcomes

Beyond cell identity, the intensity and type of mechanical stimuli also critically modulate Piezo1 signaling. Moderate activation typically maintains tissue homeostasis, whereas chronic or excessive mechanical stress often drives fibrosis.

In pancreatic stellate cells, Piezo1 responds proportionally to pressure magnitude and duration, promoting collagen and fibronectin synthesis [128]. Similarly, in dermal and cardiac fibroblasts, matrix stiffening enhances Piezo1 activation and triggers profibrotic cascades via YAP/TAZ or p38 MAPK [33, 39, 68].

In contrast, under low-intensity or regulated mechanical conditions, Piezo1 can limit fibrosis. In trabecular meshwork cells and certain macrophages populations, controlled Piezo1 activation promotes ECM turnover and immune resolution through calcium-dependent metabolic signals [122, 146]. These findings underscore that the fibrotic outcome of Piezo1 signaling hinges critically on the mechanical landscape it senses.

Microenvironmental signals modulate fibrotic bias

Finally, biochemical features of the local microenvironment further tune Piezo1's effects. In PSCs, Piezo1 activation under pressure promotes fibrosis via TRPV4 engagement and myosin-driven cytoskeletal remodeling [128]. However, under acidic conditions, as seen in PDAC, intracellular acidification suppresses Piezo1 activity, potentially limiting fibrosis [130]. In radiation-induced lung injury, Piezo1 collaborates with HIF-1α under hypoxia and inflammation to sustain TGF-β signaling and fibrogenesis [87]. These findings highlight the contextual plasticity of Piezo1, whose fibrotic potential is not fixed but shaped by dynamic biochemical cues within its niche.

Advancing Piezo1: Future directions and clinical promise

Although Piezo1 exhibits tissue-dependent and sometimes even opposing effects, certain mechanistic patterns are consistently observed. As a mechanosensor, it responds to changes in tissue stiffness and ECM composition by mediating Ca^{2+} influx, which serves as a central trigger for downstream signaling. Key pathways include MAPK, TGF-β, YAP/TAZ, and fibroblasts activation, which can lead to either pro-fibrotic or anti-fibrotic outcomes depending on the cellular context. While context-specific mechanisms remain to be fully elucidated, these shared signaling features offer a foundation for understanding its bidirectional roles in fibrosis.

Given its central role in mechanotransduction across diverse fibrotic contexts, Piezo1 is a compelling yet insufficiently characterized therapeutic target. Despite increasing interest in Piezo1 as a therapeutic target, several challenges hinder drug development. First, the large and complex structure of Piezo1, with its extensive transmembrane domains and dynamic mechanosensitive gating, makes high-resolution drug docking and allosteric site identification technically difficult [16]. Notably, docking studies by Zhang et al. revealed substantial unoccupied regions near the Yoda1 binding pocket, particularly around thiadiazole pyrazines, highlighting untapped allosteric or orthosteric sites that may be leveraged for future modulator development [152].

Currently available modulators such as Yoda1 and GsMTx4 lack selectivity, exhibit off-target effects, or are not suitable for systemic use due to stability and bioavailability limitations [157, 169, 170]. Moreover, Piezo1's broad expression in various mechanosensitive tissues raises concerns about systemic side effects, including on the cardiovascular and hematologic systems [24].

Therefore, achieving tissue-specific delivery becomes particularly important. For instance, in liver fibrosis, although Piezo1 activation in hepatic macrophages promotes disease progression, specifically targeting these cells without off-target effects remains difficult [123]. Nanoparticle or hydrogel-based strategies, as discussed previously, are still under development, but ensuring selective activation in fibrotic tissues without side effects remains a key translational hurdle.

The lack of clinically validated compounds continues to hinder *in vivo* therapeutic exploration. Future research should focus on structural mapping of ligand-channel interactions, improving pharmacokinetics via targeted delivery, and developing *in vivo* models that reflect Piezo1's bidirectional roles. Successful translation will require combining molecular specificity with spatiotemporal precision.

Conclusions

In this review, we highlight Piezo1 as a key mechanosensor in tissue fibrosis, with its bidirectional roles influenced by the mechanical microenvironment, cell type, and disease stage, making it a promising therapeutic target. To advance this field, three critical research gaps must be addressed: (i) understanding cell type-specific downstream signaling pathways mediated by Piezo1, particularly in fibroblasts and macrophages, is essential for understanding context-specific fibrotic outcomes; (ii) clarifying the mechanical stimuli, such as cyclic tension and stretch frequency, that activate Piezo1 *in vivo*, along with the associated calcium signaling dynamics, to refine therapeutic strategies; and (iii) designing high-affinity Piezo1 modulators based on structural biology and developing tissue-specific delivery methods (e.g. smart prodrugs, targeted carriers) to balance efficacy and safety. Progress in these areas requires interdisciplinary collaboration across biomechanics, structural biology, and materials science. The clinical application of Piezo1 as an anti-fibrotic strategy will usher in a new era of precision mechano-medication.

List of abbreviations

Extracellular matrix (ECM), Nuclear factor of activated T cells 1 (NFATC1), Yes-associated protein (YAP), Transforming growth factor β (TGF-β), Transcriptional co-activator with PDZ-binding motif (TAZ), Krüppel-like factor 2 (KLF2), Endothelial nitric oxide synthase (eNOS), Fibroblast growth factor 2 (FGF2), Epithelial-mesenchymal transition (EMT), Matrix metalloproteinase (MMP), Hypoxia-inducible factor alpha (HIF-1α), Vascular endothelial growth factor (VEGF), Mitogen-activated protein kinase (MAPK), Wingless/Integrated (Wnt), C-C motif chemokine ligand (CCL), Myosin light chain kinase (MLCK), Extracellular regulated protein kinases (ERK), α-smooth muscle actin (α-SMA), Discoidin domain receptor tyrosine kinase 2 (DDR2), Focal adhesion kinase (FAK), Phosphoinositide 3-kinase (PI3K), Actin-related proteins-2/3 (ARP2/3), Macrophage-to-myofibroblast transition (MMT), Ornithine aminotransferase (OAT), Arginase-1 (Arg1), Pyrroline-5-carboxylate reductase 1 (PYCR1), Proline dehydrogenase (PRODH), Hypertrophic scar (HS), Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), Reactive oxygen species (ROS), Poly-L-lactic acid (PLLA), Mechanistic target of rapamycin (mTOR), Low-frequency ultrasound electrophoresis (LFS), Interleukin (IL), Cardiac fibroblasts (CFs), Damage-associated molecular patterns (DAMPs), Valve interstitial cells (VIC), Transient receptor potential (TRP), Potassium selective Ca^{2+}- activated large conductance potassium channel (BKCa), Atherosclerosis (AS), Vascular smooth muscle cell (VSMC), Primary myelofibrosis (PMF), Megakaryocytes (MKs), Rho-associated kinase 1 (ROCK1), Radiation-induced pulmonary injury (RIPI), Alveolar type II epithelial cell (AT II), Mechanical ventilation (MV), Extracellular ATP (eATP), Airway smooth muscle cells (ASMCs), Acute respiratory distress syndrome (ARDS), B-cell lymphoma-2 (Bcl-2), A disintegrin and metalloproteinase (ADAM), Junctional adhesion molecule A (JAM-A), Airway hyperresponsiveness (AHR), Group 2 innate lymphoid cells (ILC2), Nasal polyp (NP), CC chemokine receptor 2 (CCR2), c-Jun N-terminal kinase (JNK), Bcl-2 associated X protein (Bax), Kidney renal clear cell carcinoma (KIRC), Bladder outlet obstruction (BOO), Benign prostatic hyperplasia

(BPH),Fibroblast-to-myofibroblast transition (FMT), Non-muscle myosin II A (NMIIA), Ras homolog family member A (RHOA), Oral submucous fibrosis (OSF), Pancreatic stellate cells (PSC), Transient receptor potential vanilloid 4 (TRPV4), Pancreatic ductal adenocarcinoma (PDAC), Alzheimer's disease (AD), β-amyloid (Aβ), Transient receptor potential ankyrin 1 (TRPA1), Lipopolysaccharides (LPS), Intraocular pressure (IOP), Trabecular meshwork (TM), Prostaglandin F2α (PGF2α), Sma- and Mad-related protein (SMAD), Hepatic stellate cells (HSCs), Urocortin-1 (Ucn1), Corticotropin-releasing factor receptor type 1 (CRF-R1), Tubeimoside I (TBMS1), salvianolic B (SalB), Phospholipase A2 (PLA2), Blood–brain barrier (BBB).

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Authors' contributions

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Consent for publication

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Data availability

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